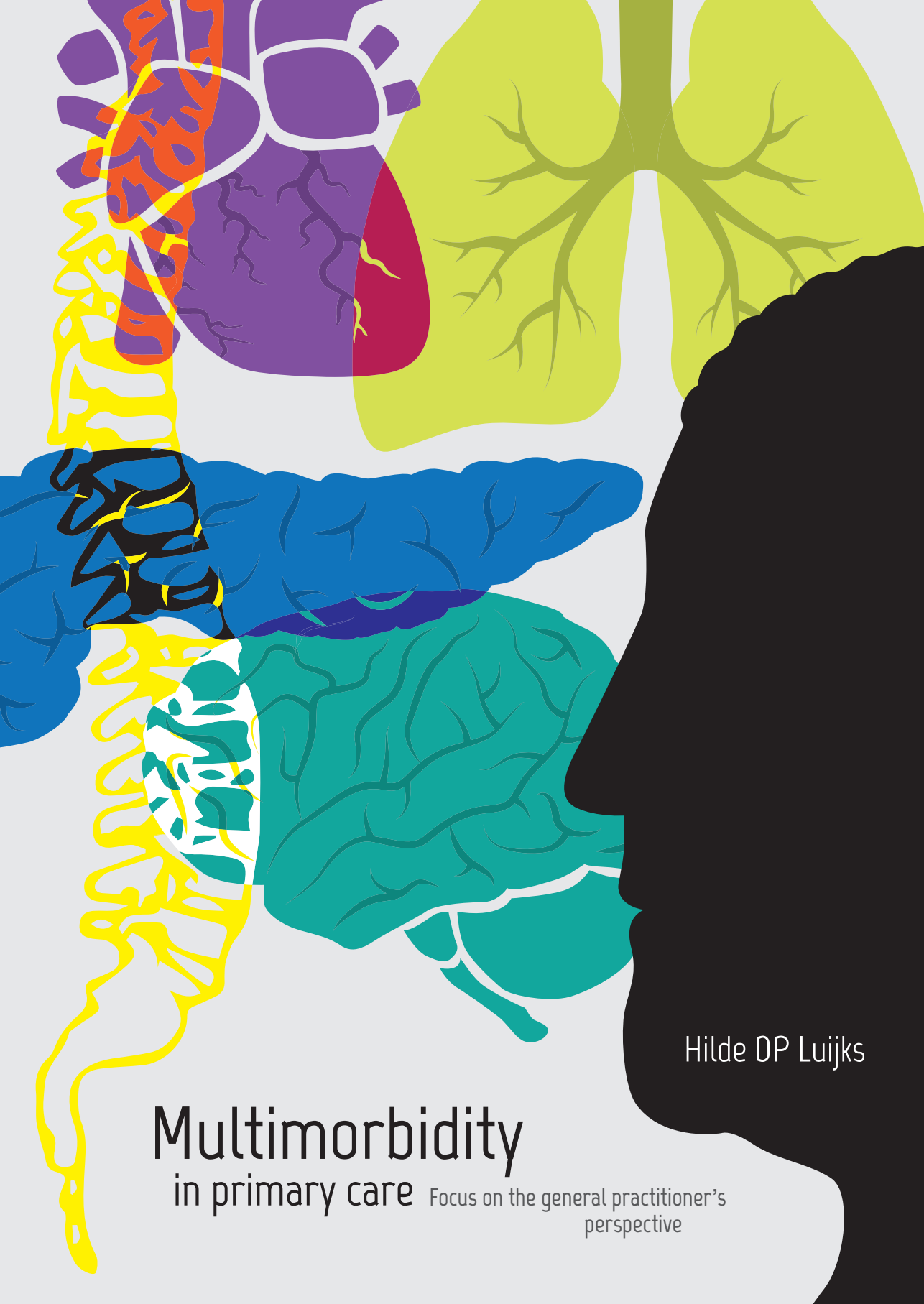

Hilde DP Luijks

Multimorbidity in primary care

Focus on the general practitioner's perspective

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Focus on the general practitioner's perspective

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Paranimfen	Dr. Y.P. Geels J.E.W. van Dijk

CONTENTS

Chapter 1

Introduction

INTRODUCTION

Multimorbidity is the co-existence of several diseases at the same time in one patient.[1, 2] In general, multimorbidity refers to chronic diseases or conditions, although some definitions also include acute or transient conditions. Different from the term 'multimorbidity', that does not specify the presence of particular diseases, 'comorbidity' refers to the presence of an additional condition in a patient with an index disease (a particular condition of interest).[1-3]

Multimorbidity is a prevalent phenomenon. Depending on which definition is applied and how many diseases are considered, most studies report a prevalence of multimorbidity around 20-30% among adult patients in primary care, with increasing percentages in ageing persons.[4-10]

Multimorbidity has negative consequences on patients' physical and mental wellbeing,[11,12] quality of life,[13-16] and mortality.[16, 17] It also has negative consequences on health care utilisation, e.g. doctor visit frequency, length of hospital stay, referral and (re)admission rates, and costs.[4, 16-19] Patients with a high morbidity burden have a higher visit frequency to specialists, even for common diseases that are normally dealt with in primary care.[20]

This Introduction will further outline some background of multimorbidity and the types of problems it brings, both to patients and practitioners. The focus of this thesis will be on the general practitioner's (GP's) perspective on multimorbidity, since this is, in contrary to the patients' perspective, relatively underexposed. By generating more knowledge on associations between specific combinations of diseases, and by applying GPs' empirical knowledge on the theme multimorbidity - thus by using mixed methods - this thesis may help to improve the care for patients with multimorbidity.

In the last two decades, attention for the phenomenon multimorbidity has clearly increased in the medical scientific literature. This is illustrated by the growing number of publications on multimorbidity over time.[21] However, the phenomenon on itself is not 'new'. Management of chronic diseases has been described as 'the very stuff of general practice'.[22] Consequently, the care for patients with multiple diseases has always been a component of primary care. Huygen's narrative and epidemiological description of the medical life histories of numerous families in his practice, published in 1978, includes descriptions of multimorbidity, although at that time not yet labelled as such.[23] Some early papers on multimorbidity provided prevalence data of comorbidity or multimorbidity in primary care, and defined its consequences for practice and research, such as limited validity of clinical trial results for patients with multimorbidity, who are generally excluded from these trials.[24, 25] This occurred shortly after the launch of 'evidence based medicine' as a new paradigm for medical practice, stressing that evidence from clinical research would become more important for clinical decision making than

intuition, pathophysiologic rationale and unsystematic clinical experience.[26] In the years that followed, evidence based medicine experienced heydays with an enormous amount of randomised trials and observational studies, resulting in large numbers of evidence-based clinical guidelines providing advice on how best to treat single diseases.

Accompanied by a growing understanding that the evidence produced under randomised clinical trial circumstances, with its focus on single diseases and often originating from secondary care, generally does not correspond to an older patient in a complex care situation, attention for multimorbidity started to increase. Not surprisingly, researchers in primary care took up a large part of this 'new' interest. After conceptualising and defining 'multimorbidity',[1] many subsequent papers on comorbidity or multimorbidity described the magnitude of this phenomenon in epidemiologic reports, mostly as retrospective or cross-sectional studies.[16, 27] Only six prospective cohort studies from five completed studies on multimorbidity in primary care were found in a systematic review.[28] A Cochrane systematic review identified ten studies examining the effect of an intervention designed to improve outcomes of patients with multimorbidity in primary care and community settings.[29] All contained a complex multi-component intervention, most addressing organisation of care, and some were patient-oriented interventions. The authors summarised that the more effective interventions to improve outcomes in patients with multimorbidity may be those focusing on particular risk factors or functional problems. It was only recently that studies of nonrandom associations of diseases started to receive more interest.[30]

Evidence-based guidelines, written for single diseases in general, do not specify how they should be used in combination, and lack recommendations on how to prioritise treatment options for patients with multimorbidity.[31-34] Advices in guidelines for a specific disease may be outright contradictory to those for another disease. The recommendations for medication prescriptions in guidelines aim to induce disease-specific benefits in patients resembling those included in randomised controlled trials.[31] If the same disease-specific benefits may be expected from implementing such treatment for patients who are older, have comorbidity, and simultaneously use other medication regimes for other diseases, remains unclear. What the advantages for patients with multimorbidity are from the combination of guideline-recommended (medication) regimes in terms of generic outcomes such as daily functioning, quality of life, or overall mortality, is completely obscure.

Presence of comorbidity may importantly influence the management of another chronic disease. Nevertheless, reports on the effects of specific comorbid diseases on the outcomes of other diseases are scarce, especially when unrelated ('discordant') diseases are considered.[34, 35] More knowledge of interactions, i.e. how one disease affects outcomes of the other when present within the same individual, is necessary to

develop evidence-based recommendations and in this way improve care for patients with multimorbidity.

In the absence of relevant and applicable evidence for patients with multimorbidity, it may be difficult for a clinician how to balance benefits and harms of all recommendations given in multiple guidelines. Moreover, it may differ between patients which outcomes contribute most to their preferred health status. Shared decision making is important and can help to target treatment at the most desirable health outcome for a particular patient. Especially in these cases it is important to incorporate patient preferences and personal circumstances in the clinical decisions made. The space that current guidelines provide to bring this into practice is limited.[33, 36]

Given the high prevalence of multimorbidity, it is not surprising that taking care of patients with multimorbidity is daily practice for general practitioners (GPs). GPs, being generalists, traditionally take care of all presented health problems without prioritising one condition over another beforehand. Multimorbidity and the existing gap in evidence-based recommendations for its management are highly relevant for GPs. They especially may perceive multimorbidity as an important and challenging problem. Best practice develops empirically in daily practice, in the absence of evidence-based medicine. Much can be learned from experiences of patients and health care providers who deal with multimorbidity on a daily basis. Qualitative research has the capacity to study experiences of illness, meanings attributed to disease, diagnosis and treatment, and reasons and considerations regarding choices made in these processes. Exactly when not much is known on a particular topic, qualitative research is ideally suited to explore the field.

Studies describing experiences of patients with multimorbidity showed that they have problems with medication management and organisation of care.[37-41] They feel a need to rely on self-care, and aim for maintenance of functional independence and management of symptoms.[42-45] This type of knowledge brings important information to doctors who aim to achieve shared decision making with their patients with multimorbidity.

Fewer papers however report on the experiences of practitioners with their care for patients with multimorbidity. The experiences that practitioners have also bring their contribution to a shared-decision making process. Some qualitative papers identified lack of time and organisational challenges as important problems for doctors in the care for patients with multimorbidity.[46-49] Previous papers paid limited attention to strategies or solutions that practitioners have developed to deal with multimorbidity in daily practice - in the absence of evidence-based guidelines to support this management. This relative lack of insight into the (general) practitioner's perspective on multimorbidity was a major reason to focus on the GP's perspective in this thesis, since it is to be expected that a large part of the outcomes of care for patients with multimorbidity is defined by the way how this is realised by doctors who deal with it on a daily basis.

AIMS OF THE THESIS

To address some important gaps in the knowledge about multimorbidity, as outlined in this Introduction, several research objectives were formulated:

- To describe the prevalence and incidence density of comorbidity in type 2 diabetes patients in primary care.
- To explore the long-term associations between comorbidity and longitudinal diabetes control parameters in type 2 diabetes in primary care.
- To study GPs' considerations and main aims in their care for patients with multimorbidity, and to explore factors influencing their management of multimorbidity.
- To explore how GPs value guidelines when applied to patients with multimorbidity, and which benefits and barriers they experience from adherence to guidelines in these patients.

OUTLINE OF THE THESIS

The results of the research questions that were formulated will be described in the following chapters of this thesis. This thesis applies mixed methods to address the research questions defined: it contains both quantitative and qualitative research.

The **first, quantitative part** takes type 2 diabetes mellitus as an example of a common chronic disease in primary care to prospectively study the effects of comorbidity on disease control parameters. Type 2 diabetes is here defined as the index disease. Since knowledge of the epidemiology of comorbidity in diabetes is essential to evaluate its effects on diabetes outcomes, but robust and representative data were lacking, **Chapter 2** starts with an investigation of the epidemiology of comorbid diseases in type 2 diabetes. In a primary care cohort of patients with newly diagnosed type 2 diabetes, the prevalence of existing chronic diseases and the incidence density of new chronic comorbid diseases over time is established. Any type of comorbidity is included, in order to provide an overview of the entire range of chronic diseases that may interfere with the diabetes management. Clusters of diseases are composed so that prevalence and incidence density can also be calculated for diseases from the same (organ) clusters.

Next, **Chapter 3** explores the long-term effects of chronic comorbidity on glycaemic control and systolic blood pressure longitudinally within the same cohort of diabetes patients in primary care. This is studied both as outcome of the total number of comorbid diseases, and as presence or absence of five specific types of comorbid diseases: cardiovascular disease, malignancy, musculoskeletal disease, mental health disease, and COPD. Potential differences in the trends of HbA1c and systolic blood pressure according to the total amount of comorbid diseases are studied for effect modification by age, sex,

body mass index, and socioeconomic status in subgroup effect analyses.
Chapter 4 specifically explores in-depth the association between comorbid COPD and longitudinal diabetes control parameter trends over five years of follow-up in the type 2 diabetes patients cohort. Differences in glycaemic and systolic blood pressure trends are compared between patients with and without comorbid COPD. In subgroup effect analyses, potential effect modification of these trends (according to presence or absence of COPD) by age, sex, body mass index, and socioeconomic status is explored.
All research in the first, quantitative part of this thesis is explorative and hypothesis-generating, without much comparable work preceding it in the literature.

The **second part** of this thesis contains **qualitative research**. It utilises the broad experience GPs have in the management of multimorbidity to explore their ideas and considerations with regard to multimorbidity, and which challenges they experience and solutions they create. Such information may importantly contribute to the knowledge in this area and shape the future research agenda. **Chapter 5** describes the main aims that GPs formulate in their care for patients with multimorbidity, which considerations they have in this respect, and their perceived facilitators and barriers in multimorbidity management. **Chapter 6** describes the value GPs attribute to medical guidelines when these are applied to patients with multimorbidity. It identifies benefits and limitations perceived from guideline adherence in these patients and ways to counteract some obstacles they come across in guideline adherence in multimorbidity. Chapters 5 and 6 contain qualitative analyses of a series of focus group interviews with Dutch GPs. Separate qualitative analyses are performed for the specific objectives of these studies, using the constant comparative analysis technique.

The general discussion of this thesis (**Chapter 7**) discusses the interpretation of the overall findings from the explorative studies in the first, quantitative part, and the qualitative results in the second part of this mixed methods thesis. It furthermore describes how these findings relate to the existing literature and what they contribute to the research field of multimorbidity in primary care. Moreover, it gives implications for practice, for future research, and for medical guidelines.

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Chapter 2

Prevalence and incidence density of chronic comorbidity in type 2 diabetes patients: an exploratory cohort study

Hilde Luijks
Tjard Schermer
Hans Bor
Chris van Weel
Toine Lagro-Janssen
Marion Biermans
Wim de Grauw

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Prevalence and incidence density rates of chronic comorbidity in type 2 diabetes patients: an exploratory cohort study

ABSTRACT

Background

Evidence-based diabetes guidelines generally neglect comorbidity, which may interfere with diabetes management. The prevalence of comorbidity described in patients with type 2 diabetes shows a wide range depending on the population selected and the comorbid diseases studied. This exploratory study aimed to establish comorbidity rates in an unselected primary care population of patients with type 2 diabetes.

Methods

This was a cohort study of 714 adult patients with newly diagnosed type 2 diabetes within the study period (1985-2007) in a practice-based research network in the Netherlands. The main outcome measures were prevalence and incidence density rates of chronic comorbid diseases and disease clusters. All chronic disease episodes registered in the practice-based research network were considered as comorbidities. We categorised comorbidity into 'concordant' (that is, shared aetiology, risk factors, and management plans with diabetes) and 'discordant' comorbidity. Prevalence and incidence density were assessed for both categories of comorbidity.

Results

The mean observation period was 17.3 years. At the time of diabetes diagnosis, 84.6% of the patients had one or more chronic comorbid disease of 'any type', 70.6% had one or more discordant comorbid disease, and 48.6% and 27.2% had three or more chronic comorbid diseases of 'any type' or of 'discordant only', respectively. A quarter of those without any comorbid disease at the time of their diabetes diagnosis developed at least one comorbid disease in the first year afterwards. Cardiovascular diseases (considered concordant comorbidity) were the most common, but there were also high rates of musculoskeletal and mental health disease. Discordant comorbid diseases outnumbered concordant diseases.

Conclusions

We found high prevalence and incidence density rates for both concordant and discordant comorbidity. The latter may interfere with diabetes management, thus future research and clinical practice should take discordant comorbidity in patients with type 2 diabetes into account.

BACKGROUND

Ageing of the population contributes to the increasing prevalence of diabetes[1-4] and of multimorbidity, that is, the co-occurrence of multiple diseases within one person.[5] The prevalence of multimorbidity is estimated at 16 to 58% in adults in primary care or population-based settings.[6-9] Diabetes mellitus (type 2 diabetes) is a chronic disease with marked effects on mortality and healthcare expenditure,[2] and its prevalence in the USA was estimated at 8% in 2010.[10]

When referring to a specific disease such as diabetes as an index condition, any co-occurring conditions are considered comorbidity.[5, 11] In primary care, over 40% of patients with diabetes also have comorbidity,[12] which is as high as 70 to 95% in selected diabetes cohorts.[13, 14] Diabetes treatment may provide lower benefit to patients with diabetes and comorbidity.[15, 16] Comorbidity has a negative effect on the quality of life of patients with diabetes,[17-20] and substantially increases their healthcare utilisation.[12, 14] It also negatively influences their self-management and emotional well-being.[21]

The number of studies on comorbidity in type 2 diabetes is limited. Previous studies focused mainly on 'concordant' comorbidity, that is, conditions that share pathogenesis, risk factors, and/or management plans with type 2 diabetes (for instance, hypertension).[22] 'Discordant' combinations,[22] that is, diseases without shared pathogenesis, risk factors, or management, remain largely unexplored. Diabetes patients with concordant and discordant comorbidity show similarly increased healthcare utilisation.[12] Recommendations for clinical approaches to comorbidity in general and of discordant combinations in particular are rarely provided in evidence-based (diabetes) guidelines.[23]

Epidemiologic descriptions of both concordant and discordant comorbidity in an unselected type 2 diabetes population may increase understanding of the heterogeneity of populations with type 2 diabetes, and may encourage consideration of co-existing discordant comorbid conditions in current type 2 diabetes management. To date, epidemiological research on comorbidity in type 2 diabetes has been limited to prevalence estimates from cross-sectional studies only. The frequency and sequence in which comorbid diseases occur may have important implications for aetiology, prognosis, and management.[11] Consequently, it would be useful to assess the prevalence and the incidence of comorbid diseases in patients with type 2 diabetes.

The aims of this study were to establish the prevalence and types of an extensive range of chronic comorbid diseases in patients with type 2 diabetes at the time of their diabetes diagnosis, and to establish the incidence density of new chronic comorbid diseases in these patients over time. We limited neither the number nor the types of chronic comorbid diseases to be studied in advance.

METHODS

Design, setting, and patients

We performed a cohort study in a population of 714 patients with newly diagnosed type 2 diabetes (patient demographics are shown in Table 1), using morbidity data from all patients with newly diagnosed type 2 diabetes from the Continuous Morbidity Registration (CMR), a practice-based research network in the Nijmegen region located in the eastern part of the Netherlands. In the Netherlands, all patients are listed with a general practitioner (GP) and receive professional healthcare through this GP. The CMR consists of four general practices, in which the GPs have been recording prospectively all episodes of morbidity for all enlisted patients from 1967 onwards, including diagnoses made by specialists after referral.[24] Diagnoses recorded in the CMR have been shown to have high validity.[25, 26] In general, longitudinal data collected in research networks such as the CMR are representative of primary care.[27] The CMR contains each patient's date of birth, gender and socioeconomic status (SES), based on the Dutch Standard Classification of Occupations,[28] classified as low, moderate, or high.[29] For many years, the total population in these practices had been relatively stable, at around 12,000 patients, with approximately 80% being adults. From 1998 onwards, the population increased steadily, reaching 14,000 in 2006.[30] Data from the CMR are representative for distribution of age, sex, and SES in the Netherlands.[30, 31]

Studies based on CMR data comply with the Code of Conduct for Health Research, which has been approved by the Data Protection Authorities for conformity with the applicable Dutch privacy legislation. For this study, approval of an external ethics committee was not required.

This explorative study period covered the years 1985 to 2007. During this period, the CMR's morbidity classification system was not changed, which enabled us to compare identical diagnoses consistently over time. Our study population had a dynamic composition, that is, observation period from start to end points varied between patients. The observation time for individual patients began with the start of the study period (1 January 1985), including for patients who had already been registered in the CMR database before 1985, or the date of a patient's enrolment as a patient in the CMR, whichever occurred first. The observation period for patients terminated either at the end of our study period (31 December 2006), or with a patient's death or deregistration from the practice, whichever occurred first. We included all adult patients (aged 18 years or over) with type 2 diabetes. The diabetes diagnosis had to be made within the study period (that is, incident cases) in accordance with universally accepted criteria,[32] and was verified in the patient's medical record when the age at the time of diagnosis was less than 45 years. Diabetes care in the CMR practices has been shown to achieve outcomes comparable with those reported under randomised controlled trial conditions.[33]

TABLE 1: Characteristics of the 714 patients included in the study

Variables	
Sex, n (%)	
Male	351 (49.2)
Female	363 (50.8)
SES,[1] n (%)	
Low	362 (50.7)
Middle	282 (39.5)
High	62 (8.7)
Missing	8 (1.1)
Age at diabetes diagnosis, years, mean (± SD, range)	
Total	63.2 (± 12.8; 21-95)[2]
Males	61.9 (± 12.8; 21-94)
Females	64.4 (± 12.7; 23-95)
Time after diabetes,[3] years, mean (± SD)	6.2 (± 4.7)[2]
Males	5.9 (± 4.5)
Females	6.6 (± 4.9)
Time before diabetes,[4] years, mean (± SD)	11.1 (± 6.3)
Time in study population, years, mean (± SD)	17.3 (± 6.0)
Year of diagnosis,[5] n (%)	
1985-1989	100 (14.0)
1990-1999	276 (38.7)
2000-2006	338 (47.3)
Reason for follow-up ending, n (%)	
End of study period	462 (64.7)
Deceased	155 (21.7)
Moved / left practice	97 (13.6)

[1]SES, socioeconomic status.
[2]Significant difference for males and females ($P < 0.05$). Non-significant sex differences not shown.
[3]Observation time in the study population after diabetes diagnosis.
[4]Observation time in the study population before diabetes diagnosis.
[5]Year of diagnosis of diabetes, classified into categories corresponding to the latest issues of the Dutch College of General Practitioner's type 2 diabetes guideline. The first, second and third issues were published in 1989, 1999, and 2006 respectively.

Comorbidity

We considered all chronic diseases as comorbidities, regardless of whether they occurred before or after the patient's diabetes diagnosis. The CMR distinguishes approximately 500 diagnostic codes (the 'E-list codes'). The GPs label each code as a new or ongoing episode for a known disease. No generally accepted definition of 'chronicity' exists, but frequently used criteria for chronicity include duration, pattern with recurrence or deterioration, and consequences on a patient's life measured by various outcomes.[34] For the current study, we defined chronic conditions as diseases (a) that are persistent (duration of 6 months or longer); (b) from which the patient does not recover; and (c) that require healthcare attention. Those conditions that did not evidently fulfil all three criteria were presented to a panel of eight experienced GPs from the CMR practices, who categorised each condition

as chronic, non-chronic or conditionally chronic. We distinguished 'conditionally chronic' diseases as those that can but do not need to have a chronic course, depending on the individual; examples are depression, asthma, and epilepsy. In these cases, the ongoing episodes at patient level defined the presence or absence of chronicity for this individual. When the expert panel unanimously judged a specific disease as chronic, we considered this particular disease as chronic in further analyses. In cases of disagreement between the panel members, the disease was labelled as conditionally chronic. In these cases, ongoing episodes at the patient level defined individual chronicity. All chronic diseases were regarded as cases of comorbidity of type 2 diabetes. The final list contained 67 chronic and 63 conditionally chronic disorders (see Appendix A).

Finally, comorbid diseases were classified into clusters, in accordance with the following chapters of *The International Classification of Primary Care* (ICPC)-1: cardiovascular, musculoskeletal, mental, eye, ear, urology, male and female genital system, respiratory, skin, digestive, endocrine and metabolic, neurologic, blood(-forming organs) and lymphatics, and general and unspecified diseases.[35] We also distinguished the subcomponents of infectious diseases and neoplasms (malignancies) as separate clusters. Small and mutually related clusters were combined into one category (see Appendix B for the cluster arrangement).

Using type 2 diabetes as the index disease, we considered all chronic diseases from the cardiovascular cluster as concordant and all other diseases as discordant comorbidity.

Statistical analysis

We calculated the prevalence of chronic comorbidity at the date of diabetes diagnosis as the number of patients with a specified (cluster of) chronic comorbidity, divided by the total number of patients, and expressed it as a proportion, with 95% confidence interval (CI). A cluster was present if at least one of the chronic diseases within this cluster had been diagnosed in an individual patient.

We also calculated the incidence density rate of chronic comorbidity for the first year before diabetes diagnosis, and for the first year, the first 5 years, and the first 10 years after diabetes diagnosis. We divided the number of new cases of (a cluster of) chronic comorbid diseases within the specified time period by the number of person-years at risk for a diagnosis of that particular comorbidity, and expressed the incidence density rate as the number of new cases per 1,000 patient-years at risk (with 95% CI). Patients who had already developed the particular comorbid disease before the specified period were no longer considered to be at risk, because a chronic disease can be diagnosed only once, and persists subsequently. For incident cases of chronic comorbidity, only the time until diagnosis of this comorbid disease contributed to the number of patient-years.

To analyse the overall burden of comorbidity in our study population, we counted the

total number of comorbid chronic diseases and clusters at the time of diabetes diagnosis, and calculated the mean and standard deviation. We also calculated the prevalence and the incidence density for having 'any' chronic comorbidity and for having three or more chronic comorbid diseases or clusters.

We tested patient characteristics for gender differences with the independent *t*-test for continuous variables and the χ^2 tests for categorical variables. In all cases, significance was set at $P \leq 0.05$. SPSS software (version 18.0; SPSS Inc., Chicago, IL, USA) supported the analyses.

RESULTS

Patient characteristics

The mean ± SD age at diabetes diagnosis was 63.2 ± 12.8 years, and the mean observation time was 17.3 ± 6.0 years. Generally, patients had a longer period before than after diabetes diagnosis within our study period. Patient age showed a normal distribution, whereas time before/after diabetes did not, with over-representation of extreme values (maximum observation time within study period). Women were generally older than men at the time of their diabetes diagnosis and had a longer follow-up, but the total observation time did not differ between women and men. Table 1 shows the patient characteristics; values are shown by sex only for those characteristics with significant sex differences.

Prevalence of chronic comorbidity at time of diabetes diagnosis

We assessed the prevalence of chronic comorbidity at the time of diabetes diagnosis (Table 2, Table 3). Only 15.4% of the patients did not have chronic comorbidity. Counting discordant diseases only (that is, excluding cardiovascular disease; CVD) showed that 70.6% (95% CI 67.2-73.9%) had at least one discordant comorbid disease in addition to type 2 diabetes.

TABLE 2: Mean ±SD number of (clusters of) chronic comorbid diseases at date of diabetes diagnosis [1,2]

	Single chronic diseases		Clusters of comorbidity[3]	
	All	Discordant only[4]	All	Discordant only[4]
Number	2.9 ± 2.4	1.7 ± 1.7	2.1 ± 1.5	1.5 ± 1.3

[1]This table describes the mean of chronic comorbid diseases present in our total population (n = 714) at the date of diagnosis of type 2 diabetes.

[2]Data are displayed both for the total count of single comorbid diseases and for the number of clusters of chronic comorbid diseases. We also distinguished 'any type' of comorbid diseases and 'discordant diseases only'.

[3]Clusters: comorbid diseases were classified into clusters, following *The International Classification of Primary Care* (ICPC)-1 chapters.

[4]Discordant: without shared pathogenesis, risk factors or management.

TABLE 3: Prevalence and incidence density of chronic comorbidity: overall, before, at time of, and after diabetes diagnosis (DD)[1,2]

Time		Extent of chronic comorbidity					
		≥1 chronic comorbid disease		≥3 chronic comorbid diseases		≥3 clusters[3]	
		All	Discordant[4] only	All	Discordant[4] only	All	Discordant[4] only
Before diabetes	ID, year before DD[5]	259.3 (169.4-349.1)	106.2 (61.8-150.6)	101.9 (69.5-134.3)	42.9 (25.0-60.8)	78.8 (52.7-104.9)	45.4 (27.6-63.3)
Diabetes diagnosis	Prevalence[6] at DD, % (95% CI)	84.6 (81.8-87.1)	70.6 (67.2-73.9)	48.6 (44.9-52.3)	27.2 (24.0-30.5)	38.0 (34.5-41.6)	22.0 (19.1-25.1)
After diabetes	ID, first year after DD[5]	263.7 (160.3-367.0)	88.3 (46.3-130.2)	80.9 (50.4-111.4)	38.9 (21.4-56.4)	48.3 (27.1-69.5)	30.4 (15.5-45.4)
	ID, first 5 years after DD[5]	160.2 (116.2-204.2)	83.9 (62.3-105.5)	91.2 (74.1-108.3)	45.1 (35.3-54.8)	59.5 (47.3-71.6)	36.3 (27.9-44.6)
	ID, first 10 years after DD[5]	142.5 (107.0-177.9)	84.5 (66.0-103.0)	84.8 (70.6-99.1)	47.7 (39.2-56.1)	62.5 (51.9-73.1)	37.6 (30.4-44.7)

Abbreviations: ID, incidence density.

[1]This table displays data on the presence and occurrence of one (the first) and of three (the third) chronic comorbid disease(s), and on the presence and occurrence of three (the third) cluster(s) of chronic comorbid disease(s) respectively.

[2]Confidence intervals (CIs) for proportions were calculated with the Mid-P exact test. CIs for person time were calculated as a normal approximation to the Poisson interval.

[3]Clusters: comorbid diseases were classified into clusters, following *The International Classification of Primary Care* (ICPC)-1 chapters.

[4]Discordant: without shared pathogenesis, risk factors or management.

[5]Incidence density displays the number of new occurrences of the specified number of chronic comorbid diseases or clusters of comorbidity, divided by the number of person-years at risk within the specified period. Expressed as number of new cases per 1,000 patient-years at risk (95% CI).

[6]Prevalence at diabetes date displays the proportion of patients in whom (at least) the specified number of chronic comorbid diseases, or clusters of comorbidity, had been diagnosed at this date.

Having three or more chronic comorbid diseases when type 2 diabetes was diagnosed was not uncommon: approximately half (48.6%; 95% CI 44.9-52.3) of the population had at least one chronic comorbid disease, and approximately a quarter (27.2%; 95% CI 24.0-30.5) had three or more discordant chronic comorbid diseases. From the prevalence data of diseases from different clusters (Table 3), it follows that this was often a heterogeneous mix of diseases.

CVDs were the most prevalent comorbid diseases at the time of diabetes diagnosis: 64.0% (95% CI 60.4-67.5, Table 4). Musculoskeletal and mental health diseases were also very common. There was a high prevalence of chronic functional somatic symptoms[36] and deafness as single diseases. Table 5 shows data on the most common chronic comorbid diseases from every cluster.

Prevalent chronic psychosis, obsessive compulsive disorder, phobia, schizophrenia, dementia, mental retardation, or Down's syndrome were combined as a heterogeneous group of chronic diseases affecting patients' mental states, which were found to affect 3.8% of the total population at time of diabetes diagnosis.

Chronic comorbidity before diabetes diagnosis

The incidence density rate of any chronic comorbidity (both concordant and discordant) in the year before diabetes diagnosis was very high (Table 3). In general, comorbid disease clusters with high prevalence rates at diabetes diagnosis also had high incidence density rates in the year before diabetes diagnosis (Table 4). For some diseases and clusters, the incidence density rate in the year before diabetes was particularly high compared with the prevalence rate at this time, and also with the incidence density rate after diabetes diagnosis. Examples are CVD (especially myocardial infarction) and male urogenital diseases (Table 4, Table 5).

Chronic comorbidity after diabetes diagnosis

In the years after diabetes diagnosis, the incidence density rate of chronic comorbidity remained high. A quarter of those without any chronic comorbid disease at the time of diabetes diagnosis developed at least one comorbid disease in the first subsequent year (263.7 new cases per 1,000 patient-years at risk, 95% CI 160.3-367.0, Table 3).

Eye and ear diseases (cataract in particular) had a high incidence density rate after diabetes diagnosis as compared with the year before diagnosis, and also compared with the prevalence rate at diabetes diagnosis: 46.9 per 1,000 patient-years at risk during the first year. Skin diseases and respiratory and endocrine diseases had a lower incidence density rate after diabetes diagnosis than before. The incidence density rate of mental health diseases was particularly low in the first year after diabetes diagnosis, with no new cases of chronic depression the first year after diabetes diagnosis (Table 4, Table 5).

TABLE 4: Prevalence and incidence density of clusters of chronic comorbidity: before, at time of, and after diabetes diagnosis (DD)[1]

	Before diabetes	Date of DD	After diabetes		
Disease cluster[2]	ID year before DD[3]	Prevalence at DD, % (95% CI)[4]	ID first year after DD[3]	ID first 5 years after DD[3]	ID first 10 years after DD[3]
Cardiovascular	176.9 (127.9-225.9)	64.0 (60.4-67.5)	122.3 (77.0-167.6)	105.5 (82.9-128.0)	101.0 (82.1-119.9)
Musculoskeletal	31.3 (15.5-47.1)	31.1 (27.8-34.6)	21.6 (8.2-35.0)	27.9 (20.1-35.8)	31.6 (24.6-38.6)
Mental health	15.2 (4.7-25.8)	24.1 (21.1-27.3)	5.8 (0.0-12.4)	10.4 (5.9-14.8)	12.6 (8.5-6.7)
Eye & Ear	29.6 (15.1-44.0)	22.7 (19.7-25.9)	46.9 (28.1-65.6)	45.3 (35.7-54.9)	42.8 (34.9-50.7)
Urogenital (male and female)	23.7 (11.3-36.1)	15.4 (12.9-18.2)	17.6 (6.7-28.5)	16.9 (11.5-22.4)	15.5 (11.2-19.8)
Urogenital[5]	26.7 (8.2-45.2)	13.4 (10.1-17.3)	14.1 (0.3-27.9)	12.8 (6.1-19.5)	14.1 (8.2-20.0)
Urogenital[6]	20.6 (4.1-37.0)	17.4 (13.7-21.5)	21.0 (4.2-37.8)	21.0 (12.4-29.6)	16.9 (10.5-23.2)
Respiratory	6.8 (0.1-13.4)	14.1 (11.7-16.9)	3.4 (0.0-8.2)	4.3 (1.6-6.9)	3.8 (1.7-5.8)
Skin	8.0 (1.0-15.1)	9.9 (7.9-12.3)	1.6 (0.0-4.8)	3.8 (1.3-6.3)	3.1 (1.3-5.0)
Digestive	3.2 (0.0-7.5)	8.5 (6.7-10.8)	3.2 (0.0-7.7)	3.7 (1.3-6.1)	4.0 (1.9-6.1)
Endocrine and metabolic	9.4 (1.9-17.0)	8.4 (6.5-10.6)	4.8 (0.0-10.3)	6.7 (3.4-9.9)	5.7 (3.2-8.2)
Malignancies	14.0 (4.8-23.1)	7.3 (5.5-9.4)	14.4 (5.0-23.7)	15.9 (10.9-20.9)	17.5 (13.2-21.9)
Neurological	1.5 (0.0-4.4)	3.4 (2.2-4.9)	1.5 (0.0-4.5)	2.0 (0.2-3.7)	1.9 (0.5-3.3)
Blood and lymphatics	4.4 (0.0-9.3)	0.4 (0.1-1.1)	0.0	1.5 (0.0-3.0)	1.6 (0.3-2.8)
Infectious	0.0	0.3 (0.0-0.9)	0.0	0.0	0.0

Abbreviations: ID, incidence density.

[1]Confidence intervals (CIs) for proportions were calculated with the Mid-P exact test. CIs for person time were calculated as normal approximation to the Poisson interval. Values smaller than 0.05 have been truncated to 0.0.

[2]Clusters: comorbid diseases were classified into clusters, after *The International Classification of Primary Care* (ICPC)-1 chapters. Sorted by decreasing prevalence at date of DD. The cluster 'general/unspecified' was removed because it contained only one case.

[3]Incidence density in a specified time period was calculated as the number of new cases of one or more diseases within a cluster of comorbidity, divided by the number of person-years at risk for a diagnosis of the particular cluster. Expressed as number of new cases per 1,000 patient-years at risk (95% CI).

[4]Prevalence at diabetes date was calculated as the number of patients with comorbidity in the cluster of interest at date of DD, divided by the total number of patients (n = 714).

[5]Prevalence and incidence density displayed only for men in the study population.

[6]Prevalence and incidence density displayed only for women in the study population.

TABLE 5: Prevalence and incidence density of chronic comorbid diseases: before, at time of, and after diabetes diagnosis (DD)[1]

Chronic disease[2]	Before diabetes	Date of DD	After diabetes		
	ID,[3] year before DD	Prevalence[4] at DD, % (95% CI)	ID,[3] first year after DD	ID,[3] first 5 years after DD	ID,[3] first 10 years after DD
Hypertension	75.2 (49.9-100.5)	38.4 (34.9-42.0)	56.8 (33.6-80.0)	42.6 (32.1-53.0)	40.0 (31.5-48.5)
Varicose veins; venous insufficiency	16.5 (5.7-27.3)	21.4 (18.5-24.6)	13.3 (3.5-23.2)	12.5 (7.6-17.4)	10.8 (7.0-14.6)
Angina pectoris	13.1 (4.0-22.2)	12.3 (10.1-14.9)	13.6 (4.2-22.9)	14.4 (9.5-19.3)	15.1 (10.9-19.3)
Atrial fibrillation / flutter	18.9 (8.2-29.7)	8.7 (6.8-10.9)	8.1 (1.0-15.2)	11.2 (7.0-15.5)	12.3 (8.6-16.0)
Myocardial infarction	17.2 (7.0-27.3)	8.5 (6.7-10.8)	4.8 (0.0-10.3)	7.8 (4.3-11.3)	9.6 (6.4-12.8)
(Congestive) heart failure	15.6 (5.9-25.3)	8.0 (6.2-10.2)	16.1 (6.1-26.1)	12.7 (8.3-17.2)	16.2 (12.0-20.4)
CVA	15.1 (5.7-24.5)	4.9 (3.5-6.7)	12.5 (3.8-21.1)	11.2 (7.1-15.4)	14.7 (10.7-18.6)
Intermittent claudication	9.0 (1.8-16.2)	4.3 (3.0-6.0)	4.6 (0.0-9.9)	4.3 (1.8-6.9)	3.5 (1.6-5.4)
TIA	8.9 (1.8-16.0)	2.9 (1.9-4.4)	4.6 (0.0-9.8)	5.5 (2.6-8.3)	5.9 (3.4-8.4)
Heart valve disease	6.0 (0.1-11.8)	2.9 (1.9-4.4)	7.6 (0.9-14.3)	5.8 (2.9-8.7)	5.6 (3.2-8.0)
Osteoarthritis, knee	14.7 (5.1-24.3)	12.0 (9.8-14.6)	6.7 (0.1-13.3)	13.9 (9.1-18.8)	13.3 (9.4-17.2)
Osteoarthritis, hip	7.9 (1.0-14.9)	8.7 (6.8-10.9)	1.6 (0.0-4.8)	3.7 (1.3-6.1)	5.4 (3.0-7.8)
Osteoarthritis, other	7.9 (1.0-14.8)	8.4 (6.5-10.6)	9.7 (1.9-17.5)	8.4 (4.7-12.0)	8.1 (5.1-11.1)
Osteoarthritis, cervical spine	6.2 (0.1-12.3)	7.1 (5.4-9.2)	4.8 (0.0-10.2)	2.4 (0.5-4.4)	2.5 (0.9-4.1)
Lumbar osteoarthritis	4.7 (0.0-9.9)	7.0 (5.3-9.1)	8.0 (1.0-14.9)	5.3 (2.4-8.2)	4.5 (2.3-6.8)
Rheumatoid arthritis; ankylosing spondylarthritis	0.0	1.4 (0.7-2.5)	0.0	0.4 (0.0-1.1)	1.0 (0.0-2.1)
(Chronic) functional somatic symptoms	5.4 (0.0-11.5)	19.2 (16.4-22.2)	3.7 (0.0-8.8)	3.8 (1.2-6.4)	3.5 (1.4-5.6)
Depression	3.0 (0.0-7.1)	2.5 (1.5-3.9)	0.0	1.2 (0.0-2.5)	1.3 (0.2-2.5)
Alzheimer's disease	7.3 (0.9-13.8)	1.5 (0.8-2.7)	3.0 (0.0-7.2)	5.0 (2.3-7.7)	7.1 (4.4-9.8)
Mental retardation	0.0	1.5 (0.8-2.7)	0.0	0.0	0.0
Deafness	16.6 (6.3-26.9)	13.6 (11.2-16.3)	13.7 (4.2-23.2)	15.5 (10.3-20.6)	13.7 (9.7-17.7)
Cataract	17.1 (7.0-27.2)	7.8 (6.0-10.0)	42.8 (26.3-59.2)	34.0 (26.4-41.6)	33.6 (27.2-40.0)
Glaucoma	3.0 (0.0-7.1)	2.9 (1.9-4.4)	3.0 (0.0-7.3)	3.1 (1.0-5.3)	2.4 (0.8-4.0)
Urinary incontinence[5]	13.1 (0.3-26.0)	13.2 (10.0-17.0)	16.6 (2.1-31.2)	17.3 (9.7-24.8)	14.7 (8.9-20.4)
Prostatic hyperplasia / hypertrophy[6]	19.3 (3.9-34.8)	9.7 (6.9-13.1)	3.4 (0.0-10.0)	8.7 (3.3-14.1)	10.4 (5.5-15.4)

Chronic disease[2]	Before diabetes	Date of DD	After diabetes		
	ID,[3] year before DD	Prevalence[4] at DD, % (95% CI)	ID,[3] first year after DD	ID,[3] first 5 years after DD	ID,[3] first 10 years after DD
Uterine fibroid[5]	0.0	2.2 (1.0-4.1)	0.0	0.7 (0.0-2.2)	0.5 (0.0-1.7)
Urinary incontinence[6]	9.0 (0.0-19.1)	2.0 (0.9-3.9)	9.4 (0.0-19.9)	5.7 (1.5-9.9)	5.1 (1.8-8.4)
COPD	3.3 (0.0-7.8)	11.2 (9.0-13.7)	1.7 (0.0-4.9)	3.7 (1.3-6.2)	3.4 (1.5-5.3)
Asthma	3.0 (0.0-7.1)	3.1 (2.0-4.6)	3.0 (0.0-7.3)	1.2 (0.0-2.5)	0.8 (0.0-1.7)
Psoriasis	4.6 (0.0-9.8)	5.6 (4.1-7.5)	1.6 (0.0-4.6)	2.0 (0.2-3.7)	1.6 (0.0-1.7)
Diaphragmatic hernia	1.5 (0.0-4.4)	2.5 (1.5-3.9)	0.0	0.0	0.3 (0.0-0.8)
Colonic diverticula; diverticulitis	1.5 (0.0-4.4)	2.0 (1.1-3.2)	3.0 (0.0-7.2)	2.3 (0.5-4.2)	2.1 (0.6-3.6)
Gout	4.5 (0.0-9.7)	4.1 (2.8-5.7)	0.0	3.5 (1.2-5.9)	3.0 (1.2-4.7)
Hypothyroidism	4.4 (0.0-9.5)	2.5 (1.5-3.9)	1.5 (0.0-4.5)	1.6 (0.0-3.1)	1.6 (0.3-2.9)
Hyperthyroidism	0.0	2.2 (1.3-3.5)	3.0 (0.0-7.2)	1.2 (0.0-2.5)	0.8 (0.0-1.7)
Breast cancer[5]	2.9 (0.0-8.7)	2.8 (1.4-4.9)	8.9 (0.0-18.9)	7.5 (2.8-12.1)	7.1 (3.4-10.9)
Prostate cancer[6]	0.0	1.7 (0.7-3.5)	6.2 (0.0-14.8)	2.4 (0.0-5.1)	3.9 (1.0-6.8)
Endometrial cancer[5]	0.0	1.4 (0.5-3.0)	2.9 (0.0-8.6)	0.7 (0.0-2.2)	0.5 (0.0-1.5)
Skin cancer	2.9 (0.0-7.0)	0.7 (0.3-1.5)	0.0	1.1 (0.0-2.4)	1.8 (0.5-3.2)
Colon cancer	0.0	0.6 (0.2-1.3)	0.0	1.5 (0.0-3.0)	2.1 (0.6-3.5)
Lung / bronchial cancer	1.5 (0.0-4.3)	0.3 (0.0-0.9)	3.0 (0.0-7.1)	1.5 (0.0-3.0)	1.8 (0.5-3.1)
Migraine	0.0	2.0 (1.1-3.2)	1.5 (0.0-4.5)	0.8 (0.0-1.8)	1.1 (0.0-2.1)

Abbreviations: DD, date of diabetes diagnosis; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; ID, incidence density; TIA, transient ischemic attack.

[1]Confidence intervals for proportions were calculated with the Mid-P exact test. Confidence intervals for person time were calculated as a normal approximation to the Poisson interval. Values smaller than 0.0 have been truncated to 0.0.

[2]Diseases sorted by cluster, in decreasing prevalence at the date of DD diabetes date, and within the particular cluster by decreasing prevalence at date of DD.

[3]Incidence density in a specified time period was calculated as the number of new cases of comorbidity, divided by the number of person-years at risk for a diagnosis of the particular comorbidity. Expressed as number of new cases per 1,000 patient-years at risk (95% CI).

[4]Prevalence at diabetes date was calculated as the number of patients with the comorbidity of interest at the date of DD, divided by the total number of patients (n = 714).

[5]Prevalence and incidence displayed only for women in the study population.

[6]Prevalence and incidence displayed only for men in the study population.

DISCUSSION

Principal findings

In this study, we established the prevalence and incidence of comorbidity in patients with type 2 diabetes. We found that 84.6% of the patients with newly diagnosed type 2 diabetes in a primary care population had at least one chronic comorbid disease at the time of their diagnosis, and both concordant and discordant comorbidity were common. Incidence density rates after diabetes diagnosis showed that rates of chronic comorbidity further increased after diabetes onset. This study clearly showed the heterogeneity of this primary care population with type 2 diabetes in terms of comorbidity.

Relation to other studies

The prevalence of comorbidity in patients with type 2 diabetes in this study was similar to[14, 37] or higher than[12, 13] those of previous studies. The number of comorbid diseases considered in a study contributes to any prevalence estimate,[7, 38] and our work had the largest number. The relatively high prevalence of comorbidity we found is more pronounced when one considers that we investigated a primary-care population including all adult type 2 diabetes patients, as opposed to studies that included only patients over 65 years of age[14, 37] or those requiring inpatient diabetes treatment.[13] Patients with discordant comorbidity outnumbered those with concordant comorbidity, a finding similar to earlier CMR-based research on comorbidity in patients with heart failure as the index disease.[39] Diabetes is not necessarily causally related to additional diseases, but co-existing chronic diseases may interfere with diabetes management in several ways.[14-20] These results encourage us to reflect on the general lack of attention to (discordant) comorbidity in evidence-based diabetes guidelines.[23]

Patients with comorbidity may prioritise one condition over another, and experience overwhelming effects of an individual disease.[21, 40] A recent study showed that physician-experienced complexity of patients with diabetes increased with prevalent discordant comorbidity, but not with concordant comorbidity, implying that improvement in diabetes management could be made merely by focusing on patient-centred rather than disease-specific interventions.[41] Patient-centred management is exactly what GPs prioritise in the management of multimorbidity;[42] however, the current tendency is to incentivise disease-specific instead of holistic care, thereby counteracting patient-centred approaches.[43-46] The extent of chronic comorbidity in patients with type 2 diabetes, as shown in the current study, urges an approach of complementing disease-specific strategies with a personalised, generalist approach for the management of patients with multimorbidity.[6, 42]

Strengths and limitations of the study

To our knowledge, this study is the first to describe the development of chronic comorbidity over time in patients with type 2 diabetes. We were able to identify comorbidity diagnosed before diabetes diagnosis. Selection of patients with a diagnosis of type 2 diabetes and all comorbidity data were based on the most reliable source, that is, physician diagnoses, rather than patient self-report[17, 37] or extraction of medication prescriptions.[47]

Diabetes in this study served as an example of a common chronic disease with standardised management plans. The objectives of this exploratory study were to establish the prevalence rates of a range of chronic comorbid conditions and their development over time. Given the nature of the CMR database, comparing comorbidity data in our diabetes population with a control group with another index disease, such as osteoarthritis, would have been possible. However, this would have distracted from the intended epidemiologic description of chronic comorbidity in type 2 diabetes patients. This study did not aim to quantify the comorbidity rate in patients with type 2 diabetes compared with patients with other chronic diseases, or to compare the rates within specific subgroups of patients with type 2 diabetes or at different time periods within the study. Considering the large number of comorbid conditions and clusters studied, such comparisons would have resulted in numerous statistically significant differences or interactions of uncertain clinical relevance. Instead, the current epidemiologic description may lead to more detailed exploration of specific conditions or subgroups for future research.

The particular strengths of the study are that the diabetes population we studied was unselected, and that we did not restrict comorbidity only to prevalent or concordant chronic diseases. Our data reflect the total burden of chronic comorbidity in patients with type 2 diabetes in general.

Currently, no universally accepted definition of 'chronic diseases' is available. Within any definition, personalisation of the concept of chronicity to the individual patient level is preferred, although often not attained.[34, 48] An Australian primary care code set applied the same criteria for chronicity as we did.[34] However, by adding the distinction of conditional chronicity based on physician-assigned ongoing episodes, we were able to personalise chronicity in our analyses. For diseases from which patients may recover (for example, depression), or for diseases with either episodic or chronic courses (for example, asthma, gout), we consider our classification comes closer to the correct description of chronicity than would a list with invariable chronic diseases.

Comments on specific comorbid diseases

Concordant comorbidity (that is, CVDs) showed the highest prevalence and incidence density rates. Although this cluster contained a large number of diseases, the main

explanation for the high rate is the concordance with type 2 diabetes. Care-related factors will have added to this finding. For instance, a GP will be more attentive for type 2 diabetes in a patient who has had a myocardial infarction. The suggestion that presence of a disease enhances attention for other diseases[49, 50] might be particularly the case for concordant combinations.

For discordant combinations also, care-dependent factors might contribute to the high rates of comorbidity. There was an evidently increased incidence of cataract in the year after diabetes diagnosis. The reason for this may be that screening for diabetic retinopathy resulted in earlier diagnosis of, or otherwise unobserved cataract diagnoses. Moreover, people might not raise certain issues until they visit their doctor for other health problems; such restraints can contribute to a higher incidence of conditions such as incontinence in the first years after diabetes diagnosis. These examples illustrate that despite the high rate of comorbidity reported, our results may still be an underestimation, as the comorbidity data refer to disease episodes truly experienced by patients and presented to their GP.

Musculoskeletal diseases have an antagonistic effect on physical exercise, which is part of the recommended treatment for diabetes.[11] Around 30% (3/10) patients with type 2 diabetes had musculoskeletal disease at time of diagnosis, and of those unaffected, an additional 32 new cases per 1,000 patient-years at risk followed during the next 10 years. These are substantial figures, which are higher than chronic musculoskeletal diseases in the overall CMR population,[30] and these cases are likely to interfere with diabetes management.

Diabetes treatment focuses on prevention of complications.[51] The presence of a malignancy may overshadow the importance of co-existing diabetes, and thus treatment priorities may alter. Dutch researchers found that patients with diabetes who had cancer received less aggressive cancer treatment than those without diabetes.[52]

Parallel to the reluctance of GPs to prescribe interventions for depression in patients with comorbidity,[53] Dutch GPs might be conservative in 'adding' a chronic mental health disease diagnosis after a diagnosis of diabetes. Including less prevalent diseases in our study enabled us to localise a heterogeneous group of patients with chronic comorbidity who possibly have difficulties in self-managing their diabetes. One in 25 patients had chronic psychosis, obsessive compulsive disorder, phobia, schizophrenia, dementia, mental retardation, or Down's syndrome when diagnosed with diabetes. A 'standard' approach to diabetes would often not respond to these patients' abilities or needs.

Conclusions

This study illustrated the complexity of the type 2 diabetes population under GP care, in terms of chronic comorbidity. We have shown that the 'straightforward' patient with

type 2 diabetes without (discordant) comorbidity is relatively rare. Management of diabetes demands management of comorbidity, including discordant diseases. Clinical guidelines have an important role in diabetes management, but their external validity may be questioned by taking comorbidity into consideration.[23, 43, 44] A patient-centred approach can be of added value in the management of patients with diabetes with chronic comorbidity.

In conclusion, this study provides new knowledge on the epidemiology of chronic comorbidity in type 2 diabetes. We hope it will inform ongoing research in this area, and is taken into account in diabetes management.

APPENDICES

Appendix A: Chronic diseases regarded as comorbidity.

Appendix B: Clusters of chronic comorbidity.

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Chapter 3

The effect of comorbidity on glycaemic control and systolic blood pressure in type 2 diabetes: a cohort study with 5 year follow-up in primary care

Hilde Luijks
Marion Biermans
Hans Bor
Chris van Weel
Toine Lagro-Janssen
Wim de Grauw
Tjard Schermer

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The effect of comorbidity on glycaemic control and systolic blood pressure in type 2 diabetes: a cohort study with 5 year follow-up in primary care

ABSTRACT

Aims

To explore the longitudinal effect of chronic comorbid diseases on glycaemic control (HbA1c) and systolic blood pressure (SBP) in type 2 diabetes patients.

Methods

In a representative primary care cohort of patients with newly diagnosed type 2 diabetes in The Netherlands (n = 610), we tested differences in the five year trend of HbA1c and SBP according to comorbidity profiles. In a mixed model analysis technique we corrected for relevant covariates. Influence of comorbidity (a chronic disease already present when diabetes was diagnosed) was tested as total number of comorbid diseases, and as presence of specific disease groups, i.e. cardiovascular, mental, and musculoskeletal disease, malignancies, and COPD. In subgroup effect analyses we tested if potential differences were modified by age, sex, socioeconomic status, and BMI.

Results

The number of comorbid diseases significantly influenced the SBP trend, with highest values after five years for diabetes patients without comorbidity ($P = 0.005$). The number of diseases did not influence the HbA1c trend ($P = 0.075$). Comorbid musculoskeletal disease resulted in lower HbA1c at the time of diabetes diagnosis, but in higher values after five years ($P = 0.044$). Patients with cardiovascular diseases had sustained elevated levels of SBP ($P = 0.014$). Effect modification by socioeconomic status was observed in some comorbidity subgroups.

Conclusions

Presence of comorbidity in type 2 diabetes patients affected the long-term course of HbA1c and SBP in this primary care cohort. Numbers and types of comorbidity showed differential effects: not the simple sum of diseases, but specific types of comorbid disease had a negative influence on long-term diabetes control parameters. The complex interactions between comorbidity, diabetes control and effect modifiers require further investigation and may help to personalise treatment goals.

INTRODUCTION

Important reasons to achieve good diabetes control are to prevent (progression of) diabetes-related complications and occurrence of cardiovascular disease.[1, 2] However, diabetes patients with extensive comorbidity may benefit less from intensive blood glucose control, which was associated with reduced 5-year incidence of cardiovascular events in an observational study, but not in patients with high comorbidity scores.[3] Comorbidity, the co-occurrence of other medical conditions in addition to a specific index disease such as diabetes,[4, 5] is a prevalent phenomenon among diabetes patients.[6-10] More than 70% have at least one chronic non-cardiovascular disease when diabetes is diagnosed.[7] Comorbidity is related to unfavourable outcomes in terms of quality of life and health care utilisation.[11-14]

Knowledge of the impact of patient characteristics such as sex,[15] socioeconomic status (SES),[16] and body mass index (BMI)[17] on the prognosis of diabetes helps in making individualised diabetes treatment plans, and its importance is increasingly recognised. Comorbidity can be regarded as yet another patient characteristic that needs to be accounted for when formulating individualised diabetes treatment targets.[2, 18] However, specific recommendations on how to take these important characteristics into account in daily practice are scarce.[19] Studies quantifying the effect of comorbidity on diabetes control in type 2 diabetes reported inconsistent findings, describing beneficial, negative, and no effects of comorbidity on diabetes control.[20-24] These studies had several limitations: they looked at a small or unclear selection of comorbid diseases only, they generally had follow-up periods of six months or less, and looked at study samples that were not representative for the overall population of patients with diabetes. These factors may contribute to differences in the results found. Particular disease combinations have received more interest in the literature, for example diabetes and depression, although the direction in their relationship and any association with diabetes outcomes remain unclear.[25] This stresses the importance to investigate the impact of comorbidity on long-term diabetes outcomes in representative samples of diabetes patients, with close monitoring of diabetes control and comprehensive recording of comorbidity. More knowledge of the types of comorbidity associated with diabetes control in 'real life daily practice' could help clinicians in further developing diabetes management, in which treatment goals better account for individual patients' comorbidity profiles.

The aim of this observational study was to explore the long-term longitudinal effects of chronic comorbid disease(s) on glycaemic control and systolic blood pressure (SBP) in an unselected primary care cohort of patients with type 2 diabetes receiving care as usual. Our primary interest was in the effect of patients' number of comorbid diseases, secondary interest in the effect of specific types of comorbid disease. We did not exclude any type of chronic comorbid disease to be studied in advance. We distinguished

comorbid diseases that are either related or unrelated to diabetes and explored the effects in different subgroups.

MATERIALS AND METHODS

Design and study subjects

We used data from a dynamic cohort of diabetes patients registered in the Continuous Morbidity Registration (CMR), a general practice registration network in the Nijmegen region, the Netherlands. These four CMR practices have been recording all morbidity that is presented to the general practitioner (GP) on a daily basis from 1967 onwards.[26] The database reflects the health care system in the Netherlands,[27] where patients are registered with a general practice and access all healthcare through that practice. GPs have an overview of all health problems of their patients. Details on the composition of our dynamic diabetes cohort are described elsewhere.[7] In short, we included all adult patients (≥ 18 years of age) with a new diagnosis of type 2 diabetes within the study's observation period (1 January 1985 to 31 December 2006). The observation time for individual patients began with the start of the study period (1 January 1985), also capturing the data from patients who had already been registered in a CMR practice before 1985, or the date of a patient's enrolment as a patient in a CMR practice, whichever occurred first. The observation period ended either at the end of our study period (31 December 2006), or with a patient's death or deregistration from the practice, whichever occurred first. The CMR contains each patient's date of birth, gender and socioeconomic status (SES), based on the Dutch Standard Classification of Occupations,[28] classified as low, moderate, or high.[29]

As part of the Nijmegen Monitoring Project (NMP), founded in 1985, the four CMR practices have also been participating in the systematic recording of diagnostic and monitoring measurements of diabetes and hypertension.[30] The NMP database includes demographic data, relevant medical history, physical diagnostics (e.g. blood pressure, weight, height), and laboratory data (e.g. HbA1c, glucose levels). Monitoring data are collected by the GPs and practice nurses during routine diabetes check-up visits 4 times per year for all diabetes patients under GP care. Since 1992, once a year a more extensive control visit includes screening for complications of diabetes and hypertension (i.e. retinopathy, nephropathy, and risk of diabetic foot ulceration). The general practices involved have shown to provide good quality diabetes care.[30]

For the current study we used data from the four practices who provide data to both the CMR and the NMP database. The CMR database provided the comorbidity data and the NMP database the diabetes control and outcome data for the same patients. Patients did not specifically consent for use of their medical data concerning the current study.

All GPs gave permission to extract data from the electronic medical records for research purposes and informed their patients, who could object to the use of their data. Those who opt-out for data extraction for research purposes continue to receive care as usual. Data are collected for observational studies and extraction from the medical records occurs de-identified. The CMR and NMP registries comply with the Code of Conduct for Health Research, which has been approved by the Dutch Data Protection Authorities (*College Bescherming Persoonsgegevens, CBP*) for conformity with the applicable Dutch privacy legislation. For this study, approval of an external ethics committee was not required.

Outcome measures

We assessed the longitudinal development of the variables of interest: HbA1c (in %; DCCT aligned - the current unit during the study period), and SBP (in mmHg). Measurement of HbA1c is performed at the annual check-up visits and samples are analysed in certified laboratories.[31] Practices retained the same laboratories throughout the study period. Blood pressure measurement is performed in the general practice at every check-up visit. Data collection from the diabetes diagnosis onwards occurred as part of routine care throughout patients' registration with the practice, thus led to longitudinal data to be collected at irregular time intervals. In order to include patients with sufficient follow-up time starting from the diagnosis, we included patients with their first measurement performed within the first four months after the diabetes diagnosis, and labelled these as baseline measurements. All subsequent measurements were also included. Patients with the first measurement more than four months after the diabetes diagnosis were excluded from further analyses.

Comorbidity

The CMR enabled us to distinguish an extensive range of comorbid diseases. Details on the recording of comorbidity are described elsewhere.[7] In short, we considered any chronic disease as comorbidity. Only chronic diseases present at the time of the diabetes diagnosis ('at baseline') were included. We classified comorbid diseases into disease clusters, in accordance with *The International Classification of Primary Care* (ICPC)-1.[32] Consequently, the effect of comorbidity could be analysed for single diseases, for patients' total number of comorbid diseases, and for clusters of diseases. The number of comorbid diseases was the main focus of this study. In the analysis of specific types of comorbidity we were particularly interested in comorbidity that is expected to interact with diabetes management in various ways: diseases that may influence GPs' and patients' priority setting regarding the healthcare provided, or patients' opportunities to adhere to lifestyle advices, and also diseases with either comparable -or conflicting-

management plans. Therefore we distinguished 'concordant' comorbidity: diseases with similar pathogenesis and disease management plans as diabetes (cardiovascular diseases in the current study).[7, 33] All other types of comorbidity were regarded as 'discordant' comorbidity (diseases unrelated to diabetes). For our longitudinal analysis we selected comorbid malignancies, cardiovascular, mental, and musculoskeletal diseases as disease clusters, and comorbid COPD as a single disease of particular interest. We refer to these selected conditions as 'selected comorbidity' from here onwards. Appendix C provides further details on the classification of disease clusters included in this study.

Because the CMR database contains longitudinal data we were able to distinguish prevalent comorbidity in a particular patient at the date of the diabetes diagnosis, and incident comorbidity after the diabetes diagnosis. For the current study we only analysed the effect of existing (prevalent) comorbid diseases on diabetes outcomes over time. The CMR's internal quality control and the extensive experience in morbidity recording before the start of our observation period ensured optimal consistency in diagnoses throughout our cohort.[26]

This paper describes the main results from a larger research project, studying the effects of a number of comorbid diseases on long-term diabetes control parameters. Description of the effects of some specific types of comorbidity on diabetes control parameters in complex interaction models fell beyond the scope of the current paper and will be reported separately.[34]

STATISTICAL ANALYSIS

SPSS (version 20.0) and SAS (version 9.02) supported the analyses. We used descriptive statistics to provide characteristics of the study population and comorbidity profiles at baseline. Differences in outcomes between male and female patients and between patients from different socioeconomic classes were compared using Chi-square tests and independent *t*-tests for categorical and continuous variables, respectively.

To address our research question we explored linear trends for both HbA1c and SBP in the five years after the diabetes diagnosis for patients with different baseline comorbidity profiles.

First we tested if the number of comorbid diseases at baseline (categorised as 0; 1 or 2; or ≥ 3) influenced the HbA1c and SBP trend. We applied a random intercept mixed model analysis using measurements nested within patients.[35] All measurements within the first five years after the diabetes diagnosis contributed to this mixed model. With the same approach we tested the potential influence of the presence of selected comorbidity. We added an interaction term 'time' by 'comorbidity' (total number, or type of comorbidity) to the model to explore differences in the HbA1c and SBP trends according to comorbidity.

Separate analyses were performed for different types of selected comorbidity. In these comparisons of diabetes patients with different comorbidity profiles, we entered sex, age at diabetes diagnosis, SES, and BMI (handled as 'last observation carried forward'[35]) as potential confounders. Values for age and BMI were handled as continuous variables in the mixed model, but we categorised them as 'low', 'intermediate', and 'high' values to facilitate (graphical) presentation of the results. The categorisation was based on the limits of the first, second (i.e., the median) and third quartile of the distribution of age and BMI values of the patients who contributed to the analysis. When exploring the effect of selected comorbidity (e.g., malignancy) on the five year HbA1c and SBP trend, 'presence of other selected comorbidity' was also entered as potential confounder.

Second, we performed subgroup effect analyses, to explore if potential differences in the trend of HbA1c and SBP, according to the number of comorbid diseases, were modified by sex, age, SES, or BMI. The confounders in the initial analysis were now tested for potential effect modification separately by adding an interaction term 'time' by 'comorbidity' by 'potential effect modifier' (e.g., 'sex') to the model. Non-significant terms were removed in a stepwise hierarchical backward elimination procedure.[35] In the cases where no significant results arose from the subgroup effect analysis, the first model (without subgroup effect analysis) defined the results.

P-values < 0.05 were considered statistically significant.

Sensitivity analysis

Since our observation period covered a lengthy time frame, we performed a sensitivity analysis to test if the calendar period in which patients' diabetes was diagnosed, influenced the findings. Diabetes diagnosis calendar period was categorised, corresponding to the prevailing diabetes guidelines (i.e., 1985-1989, 1990-1999, 2000-2006), as published by the Dutch College of General Practitioner's (publication of first, second, and third version in 1989, 1999, and 2006 respectively).[36] We performed a subgroup analysis including this variable 'calendar period'.

RESULTS

Study subjects and baseline characteristics

We identified 714 patients with a new diagnosis of type 2 diabetes within the study period (1985-2006). Outcome measurements were available in 684 patients. Of these, 610 patients had a first measurement of HbA1c and/or SBP within four months from diagnosis and were included for longitudinal analysis. Figure 1 shows a flow chart of our study population.

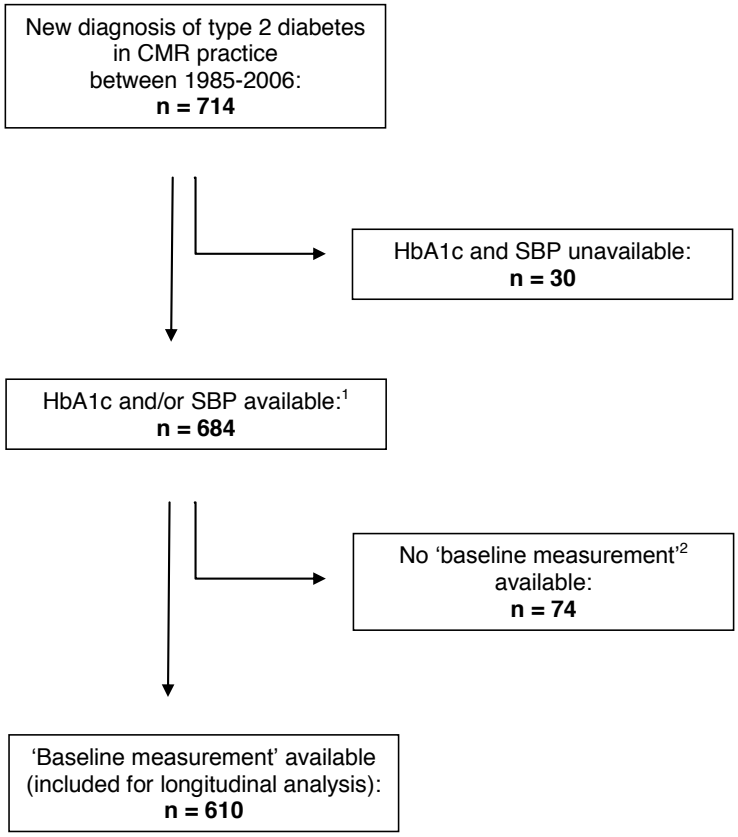


FIGURE 1: Flow chart of patient selection from the CMR general practice database

[1]Patients with the general practitioner responsible for diabetes treatment.
[2]A patient's first outcome measurements collected from a diabetes check-up visit within the first 4 months since the diabetes diagnosis was labelled as 'baseline measurement'.
CMR, Continuous Morbidity Registration.
SBP, systolic blood pressure.

Mean age at diabetes diagnosis was 63.0 (SD 12.5) years. 48.2% of the patients included were males. For some comorbid diseases the baseline prevalence differed between males and females and by SES class. Table 1 shows the baseline characteristics for the total sample, and by sex and SES separately. For both sexes the mean HbA1c at baseline was 7.4% (SD 1.7% for males, 2.0% for females). Mean SBP at baseline was 147.4 (SD 19.4) for males, 153.8 (SD 20.3) for females.

Patients without baseline measurements (n = 104, Figure 1) tended to be more often male and to have higher SES, higher age, and more comorbid diseases (including more often malignancy) at the time of their diabetes diagnosis, compared to those with baseline measurements available. None of these differences reached statistical significance.

Influence of comorbidity on the HbA1c and SBP trends

HbA1c at time of diabetes diagnosis tended to be lower when patients had a higher number of comorbid diseases at baseline, but the number of comorbid diseases at baseline did not significantly influence the longitudinal development of HbA1c ($P = 0.075$). After five years, patients without baseline comorbidity had worst glycaemic control. The number of comorbid diseases at baseline significantly influenced the development of SBP over time ($P = 0.005$). Absolute differences in mmHg were small. Patients without comorbid disease at baseline showed to have highest SBP after five years.

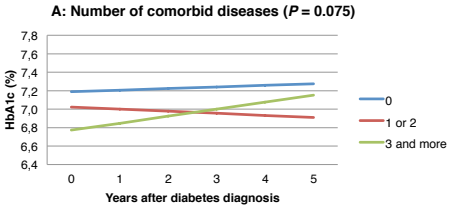
For the selected comorbidity we observed a different time trend of HbA1c for patients with *versus* without musculoskeletal disease at baseline ($P = 0.044$). Those with musculoskeletal disease started with lower HbA1c values but had higher values after five years. Cardiovascular comorbidity significantly affected the longitudinal development of SBP ($P = 0.014$), resulting in higher SBP values from the diabetes diagnosis onwards. No statistically significant effects were observed for the other types of selected comorbidity. Figures 2 and 3 present the direction of effects graphically. The lines represent the predicted values for HbA1c or SBP over five years from the mixed models. Corresponding *P*-values indicate the statistical significance of the difference between their slopes. The Figure Footnotes provide information about the definition of the 'reference category'. These Figure Footnotes also show which covariates in the models had statistically significant associations with the course of diabetes control parameters. High BMI was associated with increased HbA1c and SBP values and higher age with increased SBP values. In the analysis of the effect of selected comorbidity we corrected for presence of other selected comorbidity and found, for instance, that baseline cardiovascular disease increased SBP, and comorbid mental disease decreased both HbA1c and SBP.

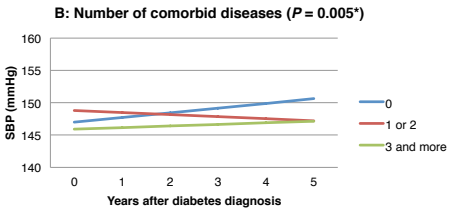
TABLE 1: Baseline patient characteristics, according to sex and SES

Variables	Total included (n = 610)	Males (n = 294)	Females (n = 316)	*P*-value[1]	Low SES (n = 315)	Middle SES (n = 242)	High SES (n = 48)	*P*-value[2]
Patient characteristics								
SES[2], n (%)								
Low	315 (52.1)	145 (49.7)	170 (54.3)					
Middle	242 (40.0)	121 (41.4)	121 (38.7)		x	x	x	x
High	48 (7.9)	26 (8.9)	22 (7.0)	0.45				
End of follow-up, reason, n (%)								
End of study period	396 (64.9)	193 (65.6)	203 (64.2)		202 (64.1)	158 (65.3)	33 (68.8)	
Deceased	128 (21.0)	62 (21.1)	66 (20.9)		64 (20.3)	55 (22.7)	8 (16.7)	
Moved / left practice	86 (14.1)	39 (13.3)	47 (14.9)	0.85	49 (15.6)	29 (12.0)	7 (14.6)	0.69
Year of diabetes diagnosis, n (%)								
1985-1989	83 (13.6)	38 (12.9)	45 (14.2)		39 (12.4)	40 (16.5)	4 (8.3)	
1990-1999	235 (38.5)	106 (36.1)	129 (40.8)		135 (42.9)	83 (34.3)	16 (33.3)	
2000-2006	292 (47.9)	150 (51.0)	142 (44.9)	0.32	141 (44.8)	119 (49.2)	28 (58.3)	0.11
Age at diabetes diagnosis, mean (SD; range), years	63.0 (12.5; 23-95)	61.9 (12.2; 24-89)	64.1 (12.7; 23-95)	0.03	61.9 (12.4; 23-91)	64.3 (12.4; 24-95)	65.2 (11.7; 32-88)	0.04
Follow-up time, mean (SD; range), years	6.2 (4.6; 0.1-21.9)	5.9 (4.4; 0.1-21.9)	6.5 (4.8; 0.2-21.2)	0.32	6.3 (4.5; 0.3-21.9)	6.4 (4.9; 0.1-20.9)	5.2 (3.6; 0.2-17.0)	0.27
Measurements per patient, total number, mean (median; SD; range)	21.8 (17.5; 18.2; 1-106)	20.1 (17; 16.3; 1-92)	23.4 (19; 19.7; 1-106)	0.02	22.1 (18; 18.2; 1-106)	22.1 (17.5; 18.7; 1-96)	19.3 (16.5; 16.7; 1-95)	0.59
BMI at baseline, mean (95%CI; SD; range), kg/m^2	29.8 (29.4-30.2; 5.1; 18.9-54.1)	29.0 (28.5-29.6; 4.5; 18.9-47.9)	30.5 (29.9-31.2; 5.5; 20.6-54.1)	<0.001	30.2 (29.6-30.8; 5.3; 19.6-52.5)	29.5 (28.8-30.1; 4.9; 18.9-54.1)	29.0 (27.7-30.4; 4.4; 20.6-43.8)	0.13
Comorbidity data								
Comorbid diseases present at baseline, mean number (SD; range)	2.8 (2.3; 0-12)	2.4 (2.1; 0-9)	3.2 (2.5; 0-12)	<0.001	2.9 (2.3; 0-12)	2.8 (2.3; 0-12)	2.5 (2.1; 0-9)	0.62
Cardiovascular comorbidity at baseline, Present, n (%)	390 (63.9)	175 (59.5)	215 (68.0)	0.03	193 (61.3)	167 (69.0)	29 (60.4)	0.14

Musculoskeletal comorbidity at baseline, Present, n (%)	197 (32.3)	78 (26.5)	119 (37.7)	0.003	102 (32.4)	79 (32.6)	16 (33.3)	0.99
Mental comorbidity at baseline, Present, n (%)	140 (23.0)	46 (15.6)	94 (29.7)	<0.001	85 (27.0)	49 (20.2)	5 (10.4)	0.02
Comorbid malignancy at baseline, Present, n (%)	42 (6.9)	21 (7.1)	21 (6.6)	0.80	25 (7.9)	13 (5.4)	4 (8.3)	0.46
Comorbid COPD at baseline, Present, n (%)	63 (10.3)	34 (11.6)	29 (9.2)	0.33	37 (11.7)	24 (9.9)	2 (4.2)	0.26
No comorbidity at baseline (0 diseases), n (%)	96 (15.7)	57 (19.4)	39 (12.3)	0.02	50 (15.9)	37 (15.3)	6 (12.5)	0.83
Cardiovascular comorbidity only at baseline, n (%)	88 (14.4)	49 (16.7)	39 (12.3)	0.13	39 (12.4)	39 (16.1)	9 (18.8)	0.31
Discordant comorbidity only at baseline, n (%)	124 (20.3)	62 (21.1)	62 (19.6)	0.65	72 (22.9)	38 (15.7)	13 (27.1)	0.06
Both concordant and discordant comorbidity at baseline, n (%)	302 (49.5)	126 (42.9)	176 (55.7)	0.002	154 (48.9)	128 (52.9)	20 (41.7)	0.32
Mental comorbidity only at baseline, n (%)	8 (1.3)	3 (1.0)	5 (1.6)	0.54	5 (1.6)	1 (0.4)	1 (2.1)	0.36
Musculoskeletal comorbidity only at baseline, n (%)	17 (2.8)	8 (2.7)	9 (2.8)	0.92	10 (3.2)	5 (2.1)	2 (4.2)	0.62
Comorbid malignancy only at baseline, n (%)	4 (0.7)	3 (1.0)	1 (0.3)	0.28	2 (0.6)	1 (0.4)	1 (2.1)	0.43
Comorbid COPD only at baseline, n (%)	4 (0.7)	3 (1.0)	1 (0.3)	0.28	3 (1.0)	1 (0.4)	0 (-)	0.62

[1]*P*-value for difference between male and female values.
[2]*P*-value for difference between low, middle, and high class of SES. Number of measurements available for SES: 605 (missing: n = 5).
SES, socioeconomic status.





Additional effects on course of HbA1c (Panel A):

Variable	Effect on HbA1c (%)	*P*-value
BMI: low	-0.07	0.004*
BMI: high	+0.10	
Age: low	+0.07	0.17
Age: high	-0.06	
Sex: female	-0.01	0.90
SES: middle	-0.09	0.72
SES: high	-0.03	

Additional effects on course of SBP (Panel B):

Variable	Effect on SBP (mmHg)	*P*-value
BMI: low	-2.4	< 0.001*
BMI: high	+3.3	
Age: low	-5.7	< 0.001*
Age: high	+4.5	
Sex: female	+1.9	0.13
SES: middle	-1.9	0.27
SES: high	+0.7	

FIGURE 2: Effect of number of comorbid diseases on five year trends of HbA1c (*P* = 0.075) and SBP (*P* = 0.005*)

The following explanations apply to Figures 2, 3, and 4.
Comorbid diseases: absence and presence are determined on the date of diabetes diagnosis.

Age and BMI categories: Based on the distribution of age and BMI values of the patients who contributed to the analysis, limits for 'low', 'intermediate', and 'high' values were 54, 64 and 72 years for age, and 26.0, 28.5 and 31.8 kg/m^2 for BMI.

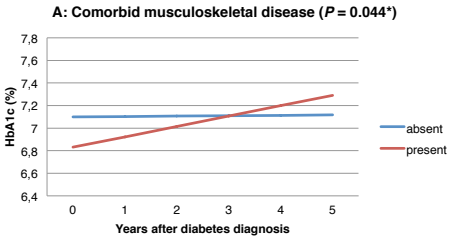
Graphs for reference categories: We define the (theoretical) combination of specific patient characteristics (e.g., sex, age, SES) as 'reference category'. In the graphic presentation, graph lines represent HbA1c or SBP trends for subjects from this 'reference category'. The additional effects tables below each graph contain information needed to construct lines of predicted outcomes, based on the mixed model results, for other subjects than the 'reference category'. It shows the additional effects (to be added to the graphs displayed above) for other covariates included in the model. These values are *not time dependent* and apply to *any of the comorbidity groups* displayed in this Figure.

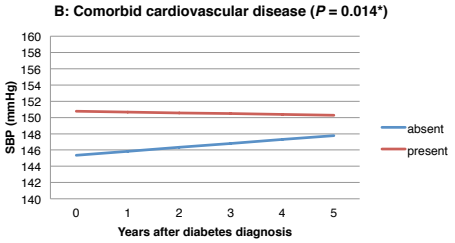
Example: Figure 3A shows predicted HbA1c time trends for patients with and without comorbid musculoskeletal disease (mixed model results). The reference category for these graph lines includes male sex. The additional effects table for Figure 3A shows an additional effect of +0.04 (% HbA1c) for female sex. This means 0.04 should be added to the blue line for female patients without musculoskeletal disease and 0.04 should be added to the red line for female patients with musculoskeletal disease. The *P*-value of 0.69 shows that this additional effect of sex on HbA1c in this analysis is not statistically significant.

Number of patients with complete contribution up to and including a specific year (follow-up ≥ *x* years) was as follows: after 0 years: 610, after 1 year: 554, after 2 years: 484, after 3 years: 430, after 4 years: 379, after 5 years: 342.

Abbreviations: BMI, Body Mass Index. SBP, systolic blood pressure. SES, socioeconomic status.
**P*-values < 0.05.

The following explanation is specific for Figure 2.
Graphs are shown for 'reference categories', i.e. male sex, low SES, median age, median BMI.





Additional effects on course of HbA1c (Panel A):

Variable	Effect on HbA1c (%)	*P*-value
BMI: low	-0.07	< 0.005*
BMI: high	+0.09	
Mental disease	-0.30	0.01*
Cardiovascular disease	-0.10	0.37
Malignancy	-0.07	0.73
COPD	0.18	0.30
Sex: female	+0.04	0.69
SES: middle	-0.08	0.77
SES: high	-0.06	
Age: low	+0.09	0.09
Age: high	-0.07	

Additional effects on course of SBP (Panel B):

Variable	Effect on SBP (mmHg)	*P*-value
BMI: low	-2.3	< 0.001*
BMI: high	+3.1	
Age: low	-5.0	< 0.001*
Age: high	+4.0	
Mental disease	-3.5	0.02*
Musculoskeletal disease	-0.2	0.84
Malignancy	-4.1	0.10
COPD	-0.3	0.08
Sex: female	+2.0	0.11
SES: middle	-2.4	0.15
SES: high	+0.1	

FIGURE 3: Effect of comorbid musculoskeletal disease on five year HbA1c trend ($P = 0.044$*) and of comorbid cardiovascular disease on five year SBP trend ($P = 0.014$*)

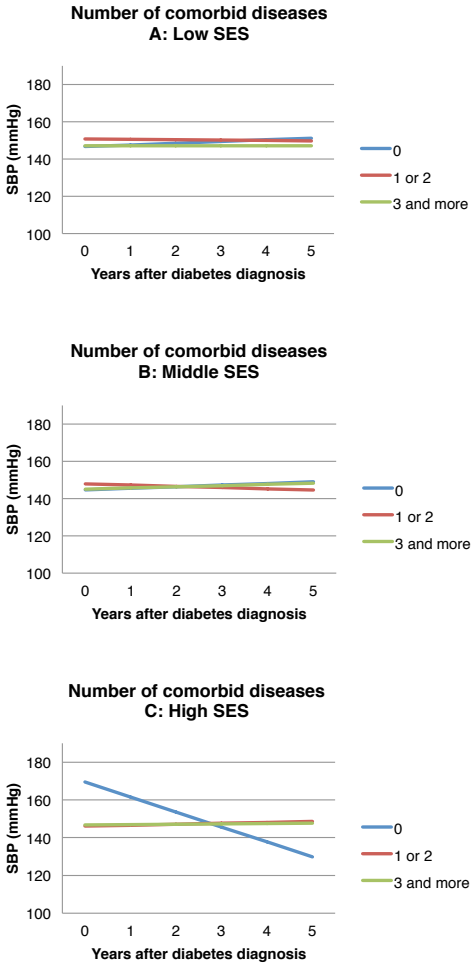
Please also see the legend from Figure 2. Graphs are shown for 'reference categories', i.e. male sex, low SES, median age, median BMI, and 'absence of other comorbidity'.

Subgroup effect analyses

In the subgroup effect analyses no modification was found for the effect of the number of comorbid diseases on the course of HbA1c. The relationship between the number of comorbid diseases at baseline and the course of SBP was significantly modified by SES ($P < 0.001$). Since the direction of effects is not readily understood in complex interaction models, Figure 4 (Panels A-C) shows the longitudinal development of SBP for subgroup differences. In the high SES group, patients without baseline comorbid diseases showed a clear decrease of SBP over time, with high baseline values and much lower values after five years. The Figure Footnotes provide information about additional effects of covariates. Note that non-significant terms were removed from the model in the hierarchical backward elimination approach.

Sensitivity analysis

No statistically significant effect modifications were found for the 'calendar period' subgroups on the effect of the number of comorbid diseases on HbA1c; or for musculoskeletal disease on HbA1c; or for CVD on SBP. We did observe a significant subgroup effect of 'calendar period' in the analysis of the number of comorbid diseases on longitudinal SBP ($P = 0.023$).



Additional effects on course of SBP, all Panels (i.e. contributing significantly to the model):

Variable	Effect on SBP (mmHg)	*P*-value
BMI: low	-2.5	< 0.001*
BMI: high	+3.4	
Age: low	-5.8	< 0.001*
Age: high	+4.6	

FIGURE 4: Subgroup effect analysis: Effect of number of comorbid diseases on five year SBP trend: modified by SES ($P < 0.001$*).

Please also see the legend from Figure 2. Graphs are shown for median age and median BMI. Other variables are specified.

DISCUSSION

In this observational study we explored the effects of chronic comorbid diseases on the long-term longitudinal development of HbA1c and SBP in newly diagnosed type 2 diabetes patients in primary care. Our results show that the number of comorbid diseases at baseline influenced longitudinal development of SBP, an effect that was modified by SES. The effect of comorbidity on the longitudinal development of HbA1c was limited, but present in specific types of discordant comorbidity (musculoskeletal disease). Concordant cardiovascular comorbidity negatively impacted on the longitudinal SBP development. These results indicate that comorbid diseases affect long-term diabetes control parameters, with distinct patterns for different numbers and types of comorbidity, and modification of some patterns by SES. The specific information on the relation between comorbidity and diabetes control parameters provided by this explorative study needs replication first, but has the potential to offer new opportunities to deliver more personalised diabetes treatment, by taking specific types of comorbidity into account that may require different therapeutic approaches.

Our longitudinal data cover a lengthy study period, which is a major strength of this work. By deliberately including patients of all ages and with any type of comorbidity, our data are representative for the diabetes population in primary care. The data have their origin in an experienced general practice registration network and practices provide good quality diabetes care. The diabetes control parameters we used (HbA1c and SBP) are relevant when studying long-term diabetes control. Surrogate outcomes such as 'intensification of medication treatment' reflect mainly physicians' actions, not patients' responsiveness, and do not necessarily result in better diabetes control.[22-24] Since we only included newly diagnosed diabetes patients, comparison of diabetes control parameters over time was meaningful.

During this study period, diagnosis and treatment of some diseases studied may have changed, which could influence our findings – although it is not obvious if this would alter our findings in a specific direction, or if this would only be the case for specific types of comorbidity. This type of limitation is inherent to analysing longitudinal data with an extensive follow-up period. In a sensitivity analysis, only the association between the number of comorbid diseases and SBP trend was significantly affected by the calendar period of the diabetes diagnosis. Exploration of this association suggested that this resulted from altered treatment of diabetes itself throughout our study period – not changes in categorising or managing 'comorbidity'. After all, monthly meetings ensured maximum consistency in CMR's diagnostic labels, which are known for their high validity.[37, 38]

The extensiveness of our data did not allow for detailed elaboration on complex subgroup effect analyses results for various types of comorbid diseases within the current paper.

Although we had smaller numbers of repeated measurements available for HbA1c than for SBP, in further subgroup effect analyses we observed that comorbid malignancy (the smallest group of selected comorbidity) had significant effects on the HbA1c trend of diabetes patients, with modification by some effect modifiers (to be reported separately). This makes lack of statistical power an unlikely explanation for the limited effects of comorbidity on HbA1c development observed in this study.

Among the 30 patients in our cohort without outcome data, some had not been included in the NMP registration due to extensive multimorbidity. These patients should be regarded as seriously ill patients with comorbid diabetes, in whom low priority was given to the diabetes monitoring. Some other patients without outcome measurements had their diagnosis of diabetes assigned towards the end of our study period, allowing insufficient time for the first outcome measurement registration to occur in the NMP database within the study period. Any potential bias here is probably small, since no statistically significant differences in baseline characteristics were observed between patients with and without baseline measurements. The higher proportion of diabetes diagnoses made at the end of our study period may be caused by increased attention to early detection of diabetes and by targeted screening for diabetes in the same period.[39] Due to the extensive length of the study period this did not result in insufficient long-term follow-up data.

Inclusion of lipids as diabetes control parameter would have provided added value to this study. However, after the first recognition of the importance of lipid regulation in diabetes,[40] the revised version of the Dutch College of General Practitioners diabetes guideline in 1999 resulted in increased attention to the role of lipids halfway our study period. We decided to look at one glycaemic and one major cardiovascular risk outcome measure only - which already resulted in an extensive dataset.

The longitudinal outcomes are obviously influenced by prescribed medication and non-pharmacological interventions for the treatment of diabetes and comorbid diseases. In this dynamic cohort study, it was not possible to compare pharmacotherapy and lifestyle interventions longitudinally between diabetes patients with and without specific types of comorbidity. Therefore, we cannot tell if and how potential differences in therapeutic regimes may have contributed to the outcomes observed. However, such a comparison fell beyond the scope of this observational, explorative study, in which we aimed to explore the long-term associations between comorbidity and diabetes control parameters in patients receiving care as usual. The presence of comorbidity may influence GPs' perception of benefits and feasibility of therapeutic regimes.[41, 42] Specific types of prescriptions may be less appropriate or less safe in patients with particular types of comorbidity, which may influence the diabetes treatment options for these patient groups. Future longitudinal research should pay attention to the role of medication

prescriptions in the association between diabetes control parameters and comorbidity. Prescription data may be handled as a potential confounder, or even as an outcome measure.

We used a well-documented, comprehensive definition of comorbidity to describe the effect of comorbidity on trends of diabetes control parameters in diabetes patients. The study design enabled accurate distinction between 'no', 'some' (one or two) and 'many' (three and more) comorbid diseases. This contrasts with other studies in which comorbidity could be either present or absent in a limited selection of diseases, where absence of selected comorbidity does not exclude presence of unselected types of comorbidity.[21-23] We made a clinically important distinction between related (concordant) comorbidity and unrelated (discordant) comorbidity.[33] The slightly better long-term outcomes for SBP and HbA1c for patients with 'much' comorbidity (≥ 3 diseases at baseline) compared to patients without comorbidity (0 diseases) are new findings that need further investigation. Different types of comorbidity appeared to affect diabetes outcomes in different ways.

The mixed model analysis technique we used was the most appropriate model to address our research question, and enabled us to optimally use the available longitudinal data. Absolute values of HbA1c and SBP are difficult to interpret in this study since the mixed model reports predicted values for specific (reference) groups. We deliberately formulated a broad research question. Our results should be regarded as a starting point for further research, hence care must be taken not to 'over-interpret' the results before they are confirmed in larger cohorts with deeper investigation of prominent associations found.

Little is known about the long-term 'natural development' of HbA1c and SBP in type 2 diabetes patients from the diabetes onset onwards. Best estimations of this 'natural course' probably come from control groups of large diabetes trials, of which only UKPDS[43] included newly diagnosed patients, but they excluded patients with 'serious illness'. Our findings, showing different longitudinal outcomes according to the absence or presence of (particular types of) comorbidity, add knowledge on the 'natural development' of diabetes outcomes from diabetes diagnosis onwards, and especially how they are influenced by comorbidity and other effect modifiers. In other words, it showed that long-term diabetes control parameters in patients without comorbidity (typically the patients that are included in RCTs) are not representative for the entire diabetes population. Studies that look at the effectiveness of diabetes treatment but overlook comorbidity may have seriously limited generalisability of their results.

Detection of type 2 diabetes may occur in an earlier stage of the disease if comorbidity is present. The lower baseline values shortly after the diabetes diagnosis among patients with musculoskeletal disease (for HbA1c) or with 'three and more' comorbid diseases (HbA1c and SBP) compared to those without comorbidity suggest existence of such patterns. It

may occur for example by more frequently performed laboratory tests including glucose levels in patients who already have other chronic diseases. In the group with pre-existing musculoskeletal comorbidity, HbA1c increased in subsequent years, resulting in worse glycaemic control after five years compared to patients without musculoskeletal disease at baseline. Impaired ability for physical exercise seems a plausible explanation for the longitudinal differences. Similarly, we assume that the consistent additional effects from comorbid mental disease (reduced HbA1c and SBP values) is explained by a higher contact frequency of these patients with their GP,[44] resulting in additional opportunities to diagnose and treat diabetes in an early stage with slightly better outcomes. The nature of comorbid cardiovascular disease, concordant with diabetes, probably explains its augmenting effect observed for SBP. It should be noted that patients with cardiovascular disease might be diagnosed with 'hypertension'. However, the presence of the diagnostic label 'hypertension' alone (without presence of other cardiovascular disease, such as myocardial infarction or CVA) did not classify as 'cardiovascular disease' in the longitudinal analysis for the current study, and therefore 'hypertension' could be diagnosed also among the patients in the group 'without cardiovascular disease'. Diabetes guidelines recommend good SBP control in 'all' diabetes patients - independent from presence of (cardiovascular or non-cardiovascular) comorbidity.[1, 2] In this observational study we analysed whether presence of particular numbers or types of comorbidity was associated with the attainment of different longitudinal diabetes control parameters in diabetes patients receiving care as usual from their GP. From this objective, the impossibility to correct for use of antihypertensive medication is of minor importance since, according to current guidelines, lowering SBP if values are increased is regarded as equally important in all patients.

A large number of comorbid diseases at baseline (three and more) did not result in a less favourable course of HbA1c and SBP, but particular types of comorbidity did. This observation - not the simple sum of diseases, but specific types of comorbid disease influence the course of diabetes control parameters - emphasises that the diabetes care as provided by GPs is part of general healthcare delivered to 'whole persons', i.e. 'person-centred care'. Apparently, the patient-specific context intervenes, in which GPs integrate disease-specific and generic patient characteristics and treatment goals as part of diabetes-specific care.

The observed effect modification of the number of comorbid diseases on the course of SBP by SES warrants further exploration. Other studies already highlighted SES as an important patient characteristic in comorbidity[6] and in diabetes research,[16] but little has been reported on its role as effect modifier as described here. Further subgroup effect analysis from our own data showed that SES also modifies the effect of long-term SBP control compared between diabetes patients with and without comorbid COPD.[34] The

explorative design of the current study does not allow us to give possible explanations, such as patients' delay (to visit a doctor) or greater ability for long term risk factor control among specific SES groups.

In conclusion, this observational study showed that presence of chronic comorbid diseases affected the longitudinal course of HbA1c and SBP in a representative sample of newly diagnosed type 2 diabetes patients receiving care as usual. Different numbers and types of comorbid diseases showed specific patterns of influence on these outcomes. Further investigation of the complex association between diabetes, comorbidity and effect modifiers is needed to replicate our findings and to elaborate on the consequences of specific levels of diabetes control. Our observations illustrate that future diabetes studies should take the presence of comorbidity into account, and suggest that GPs' diabetes care requires a person-centred approach, especially when comorbidity is present.

APPENDICES

Appendix C: Classification of comorbidity.

ACKNOWLEDGEMENTS

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Chapter 4

Exploring the impact of chronic obstructive pulmonary disease (COPD) on diabetes control in diabetes patients: a prospective observational study in general practice

Hilde Luijks
Wim de Grauw
Hans Bor
Chris van Weel
Toine Lagro-Janssen
Marion Biermans
Tjard Schermer

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Exploring the impact of chronic obstructive pulmonary disease (COPD) on diabetes control in diabetes patients: a prospective observational study in general practice

ABSTRACT

Background

Little is known about the association between COPD and diabetes control parameters.

Aims

To explore the association between comorbid COPD and longitudinal glycaemic control (HbA1c) and systolic blood pressure (SBP) in a primary care cohort of diabetes patients.

Methods

This is a prospective cohort study of type 2 diabetes patients in the Netherlands. In a mixed model analysis, we tested differences in the 5-year longitudinal development of HbA1c and SBP according to COPD comorbidity (present/absent). We corrected for relevant covariates. In subgroup effect analyses, we tested whether potential differences between diabetes patients with/without COPD were modified by age, sex, socioeconomic status (SES) and body mass index (BMI).

Results

We analysed 610 diabetes patients. A total of 63 patients (10.3%) had comorbid COPD. The presence of COPD was not significantly associated with the longitudinal development of HbA1c ($P = 0.54$) or SBP ($P = 0.33$), but subgroup effect analyses showed significant effect modification by SES ($P < 0.01$) and BMI ($P = 0.03$) on SBP. Diabetes patients without COPD had a flat SBP trend over time, with higher values in patients with a high BMI. For diabetes patients with COPD, SBP gradually increased over time in the middle- and high-SES groups, and it decreased over time in those in the low-SES group.

Conclusions

The longitudinal development of HbA1c was not significantly associated with comorbid COPD in diabetes patients. The course of SBP in diabetes patients with COPD is significantly associated with SES (not BMI) in contrast to those without COPD. Comorbid COPD was associated with longitudinal diabetes control parameters, but it has complex interactions with other patient characteristics. Further research is needed.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is typically diagnosed in middle-aged subjects who also have an increased risk for other chronic conditions.[1] The presence of other diseases in addition to an 'index disease' is defined as comorbidity.[2] Among patients with mild-to-moderate COPD, the main causes of death are comorbid diseases such as lung cancer and cardiovascular diseases.[3] COPD has a large impact on morbidity and mortality.[4]

Another example of a chronic disease with marked effects on global health and health care is type 2 diabetes.[4,5] Of all patients with COPD, 9-13% of the patients have comorbid diabetes,[6–9] and 4-13% of patients with diabetes have comorbid COPD.[9–11] Although these numbers originate from different studies and consequently are not directly comparable, they clearly illustrate that the combination of COPD and diabetes is a rather common one.

In recent years, knowledge and awareness of the importance of patient-specific factors in the treatment of COPD[12] and diabetes[13] has grown, resulting in an increased tendency to individualise disease management. An important characteristic of a patient with a specific chronic disease, such as COPD, is the comorbidity that may also be present. However, current guidelines for COPD and diabetes have limited applicability for patients with comorbid conditions.[14] Very little is known on how the presence of a specific disease, such as COPD, influences the long-term outcomes of another disease, such as diabetes. This type of information is important if health care professionals aim to personalise disease management plans for COPD and diabetes patients. In addition, other characteristics such as age, sex, body mass index (BMI) and socioeconomic status (SES) may have well-known effects on COPD[15–17] and on diabetes,[18,19] but how they interact if both diseases are present in one and the same patient is unknown. Detailed data on comorbidity, patient characteristics, and disease control parameters from a representative patient population may inform us about the interaction between the two diseases and the impact on patients' prognosis.

The aim of this explorative, hypothesis-generating paper was to investigate the association between COPD as a comorbid condition and longitudinal diabetes control parameters in patients with type 2 diabetes in primary care. We also explored the role of sex, age, BMI and SES in the relationship between COPD and diabetes control.

MATERIALS AND METHODS

Design and study subjects

We used available data from a dynamic prospective cohort of diabetes patients registered in the Continuous Morbidity Registration (CMR), a general practice registration network in the Nijmegen region, the Netherlands. The four practices constituting the CMR have been recording all morbidities that are presented to the general practitioners (GPs) on a daily basis since 1967.[20] The database reflects the health care system in the Netherlands,[21] where patients are registered with a general practice and have access to specialist care through that practice. In this system, where GPs receive capitation payment, the nature of medical conditions or treatment does not influence the GPs' performances. Details on the composition of our diabetes cohort are described elsewhere.[10] In short, we included all adult patients with a new diagnosis of type 2 diabetes within the observation period of the study (1 January 1985 to 31 December 2006). Time from the start to the end of observation varied between patients, beginning with either the start of the study period or the date of a patient's enrolment in a CMR practice. The observation period ended either at the end of our study period or with a patient's death or deregistration from the practice.

All four CMR practices also participate in the so-called 'Nijmegen Monitoring Project' (NMP),[22] which was initiated in 1985 to systematically record diagnostic and monitoring measurements of patients with diabetes and/or hypertension. The NMP database includes demographic data, physical diagnostics (e.g., blood pressure, weight, height) and laboratory data (e.g., HbA1c, glucose levels). Monitoring data are collected by the GPs and practice nurses during routine 3-monthly diabetes check-up visits for all diabetes patients under GP care. The practices involved have been shown to provide good-quality diabetes care.[22] We linked data from these two databases to study the effects of chronic comorbidity (data originating from the CMR) on the course of diabetes control over time (data from the NMP). The current paper presents results from the effect of COPD, as selected comorbid disease, on longitudinal diabetes control parameters, and effect modification by a number of patient characteristics in subgroup effect analyses. This analysis is part of a larger project studying the effects of different types of comorbid diseases on diabetes control parameters.

The CMR and NMP registries comply with the Code of Conduct for Health Research, which has been approved by the Data Protection Authorities for conformity with the applicable Dutch privacy legislation. For this study, approval of an ethics committee was not required.

Selection of COPD and other comorbidities

The presence of COPD was identified as a doctor diagnosis recorded in the CMR database. The CMR has previously been used to study cohorts of patients with COPD,[23,24] and the diagnoses correlate well with spirometry results.[25] Details on the recording of comorbidity have been reported in a previous paper.[10] We selected comorbid COPD as a single disease of particular interest for the analysis of possible associations between comorbid conditions and the course of diabetes control parameters, and we were, in addition, interested especially in comorbid malignancies and cardiovascular, mental, and musculoskeletal diseases.

Study outcomes

HbA1c (in %, the current unit during our study period) and systolic blood pressure (SBP, in mmHg) were the primary study outcomes. Measurement of HbA1c is performed at the annual check-up visits. Blood pressure measurement is generally performed at every check-up visit. To include patients with sufficient follow-up starting from the diagnosis, we only included patients with their first measurement performed within the first 4 months after the diabetes diagnosis and labelled these as 'baseline measurements'. All subsequent measurements were regarded as repeated measurements for individual patients and contributed to the longitudinal analysis. We studied the development of these outcomes during the 5-year follow-up.

Statistical analysis

SPSS (version 20.0) and SAS (version 9.02) software supported the analysis. Characteristics of the study population are provided using descriptive statistics. We compared linear trends for both HbA1c and SBP in the 5 years after the diabetes diagnosis between patients with and patients without comorbid COPD. We applied a random intercept mixed model analysis using measurements nested within patients.[26] In this model, the presence of existing COPD, i.e., recorded before the diabetes diagnosis, was the variable of interest. We added an interaction term 'time' by 'COPD' (absent/present) to the model to explore differences in HbA1c and SBP trends according to the absence or presence of COPD. In this comparison between patients with and without COPD, we entered sex, age at diabetes diagnosis, SES, BMI (handled as 'last observation carried forward'[26]) and the presence of other comorbidities (as specified above) as potential confounders. Values for age and BMI were handled as continuous variables in the mixed model, but we categorised them as 'low', 'intermediate' and 'high' values to facilitate (graphical) presentation of the results. The categorisation was based on the limits of the first, second (i.e., the median) and third quartiles of the distribution of age and BMI values of the patients who contributed to the analysis.

Furthermore, we performed subgroup effect analyses to test whether potential differences in the HbA1c and SBP trends between diabetes patients with or without comorbid COPD were modified by sex, age, SES, or BMI. The confounders in the initial analysis were now tested for potential effect modification separately by adding an interaction term 'time' by 'COPD' (absent/present) by 'potential effect modifier' to the model. Nonsignificant interaction terms were removed in a stepwise backward elimination procedure.[26] In these subgroup effect analyses, we added the presence of other comorbidities as potential confounders (not as potential effect modifiers). In cases in which no significant results arose from the subgroup effect analysis, the first model (without subgroup effect analysis) defined the results.

Not only comorbid COPD already present at the study start may be associated with the longitudinal diabetes outcomes, the same may be the case for incident COPD after the patient's diabetes diagnosis. Therefore, we performed sensitivity analyses excluding the patients who did not have COPD at their diabetes diagnosis date but who were diagnosed with COPD during the 5-year follow-up.

A *P*-value < 0.05 was considered statistically significant.

RESULTS

Study subjects and baseline characteristics

Figure 1 shows a flowchart of our study population. We included 610 patients with a mean age of 63 years (SD 12.5, Table 1) for longitudinal analysis. In all, 63 patients (10.3%) had comorbid COPD at the date of their diabetes diagnosis, and another 8 patients were diagnosed with COPD during the 5-year follow-up period. Patients with pre-existing COPD were older and had more additional comorbid conditions, apart from COPD, compared with patients without COPD (i.e., musculoskeletal disease, 51 vs. 30%). Note that in the longitudinal analyses we corrected for the presence of selected comorbidity.

Influence of comorbid COPD on the course of HbA1c and SBP

After correction for covariates, comorbid COPD was not significantly associated with the course of HbA1c ($P = 0.54$) or SBP ($P = 0.33$) values over time in the initial analyses. Figure 2 shows the time trends for patients with and without comorbid COPD and the additional effects of covariates. The Figure Footnotes provide information for the definition of the 'reference category'.

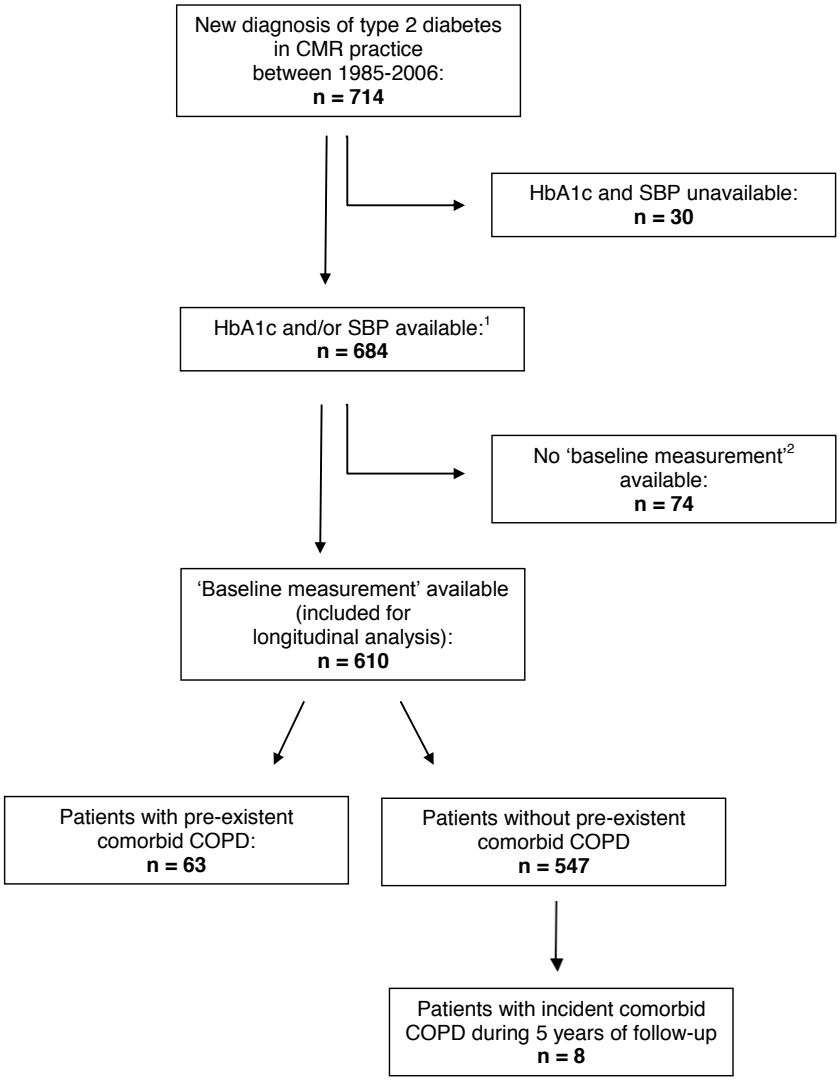


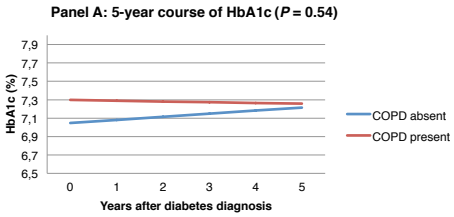
FIGURE 1: Flow chart of patient selection from the CMR general practice database

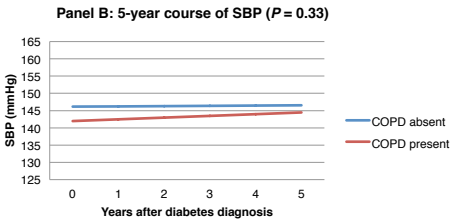
[1]Patients with the GP responsible for diabetes treatment.
[2]A patient's first outcome measurements collected from a diabetes check-up visit within the first 4 months since the diabetes diagnosis was labelled as 'baseline measurement'.
CMR, Continuous Morbidity Registration; COPD, chronic obstructive pulmonary disease; GP, general practitioner; SBP, systolic blood pressure.

TABLE 1: Baseline characteristics of patient population, according to the presence / absence of COPD

	Total included n = 610	COPD present[1] n = 63	COPD absent[1] n = 547	*P*-value[1]
Patient characteristics				
Sex: male, n (%)	294 (48.2)	34 (54.0)	260 (47.5)	0.33
Age at DM diagnosis, years; mean (SD)	63.0 (12.5)	69.0 (11.0)	62.3 (12.5)	< 0.001
Follow-up time, years; mean (SD, range)	6.2 (4.6; 0.1-21.9)	4.1 (3.6; 0.3-15.6)	6.5 (4.7; 0.1-21.9)	< 0.001
Measurements per patient, total number, mean (median; SD; range)	21.8 (17.5; 18.2; 1-106)	15.7 (10; 14.9; 1-86)	22.5 (19; 18.4; 1-106)	0.001
BMI at baseline,[2] mean (SD), kg/m^2	29.8 (5.1)	29.5 (5.2)	29.8 (5.1)	0.57
SES,[2] n (%)				
Low	315 (52.1)	37 (58.7)	278 (51.3)	0.26
Middle	242 (40.0)	24 (38.1)	218 (40.2)	
High	48 (7.9)	2 (3.2)	46 (8.5)	
Year of diabetes diagnosis, n (%)				
1985-1989	83 (13.6)	3 (4.8)	80 (14.6)	0.07
1990-1999	235 (38.5)	24 (38.1)	211 (38.6)	
2000-2006	292 (47.9)	36 (57.1)	256 (46.8)	
Comorbidity data				
Comorbid diseases,[3] mean number (SD; range)	2.7 (2.3; 0-11)	4.0 (2.5; 0-11)	2.6 (2.2; 0-11)	< 0.001
Comorbid diseases,[3] (categorised), n (%)				
0	100 (16.4)	4 (6.3)	96 (17.6)	0.002
1 or 2	227 (37.2)	17 (27.0)	210 (38.4)	
3 and more	283 (46.4)	42 (66.7)	241 (44.1)	
Cardiovascular comorbidity,[3] present, n (%)	390 (63.9)	44 (69.8)	346 (63.3)	0.30
Musculoskeletal comorbidity,[3] present, n (%)	197 (32.3)	32 (50.8)	165 (30.2)	0.001
Mental comorbidity,[3] present, n (%)	140 (23.0)	18 (28.6)	122 (22.3)	0.26
Comorbid malignancy,[3] present, n (%)	42 (6.9)	4 (6.3)	38 (6.9)	0.86
Incident comorbid COPD after DM diagnosis,[4] n (%)	12 (2.0)	NA	12 (2.2)	NA
Incident COPD in first year after DM diagnosis, n (%)	1 (0.2)	NA	1 (0.2)	NA
Incident COPD in first five years after DM diagnosis, n (%)	8 (1.3)	NA	8 (1.5)	NA

Characteristics of patients at baseline, i.e., at the date of the diabetes diagnosis.
Abbreviations: BMI, body mass index; DM, type 2 diabetes mellitus; NA, not applicable; SES, socioeconomic status.
[1]COPD presence/absence: assessed on the date of diabetes diagnosis. *P*-values displayed are calculated for the difference between the group with *versus* without comorbid COPD. We performed Chi-square tests for continuous variables and independent *t*-tests for continuous variables. *P*-values < 0.05 were considered statistically significant.
[2]Number of measurements available for BMI at baseline: 576 (missing at baseline: n = 34). Number of measurements available for SES at baseline: 605 (missing at baseline: n = 5).
[3]Presence of any type of comorbid disease was assessed at the date of diabetes diagnosis. For the diabetes patients with comorbid COPD present at the diabetes diagnosis date, we excluded COPD in the count of the total number of comorbid diseases to make a meaningful comparison with the total number of comorbid diseases in patients without COPD.
[4]Mean time (after the diabetes diagnosis date) until the date of comorbid COPD diagnosis, for incident cases, is 4.6 years.





Additional effects on course of HbA1c (Panel A):

Variable	Effect on HbA1c (%)	*P*-value
Female sex	+0.04	0.70
Middle SES	-0.08	0.77
High SES	-0.05	
Low BMI	-0.07	<0.01*
High BMI	+0.09	
Young age	-0.07	0.08
Old age	+0.07	
Comorbid malignancy present	-0.07	0.75
Comorbid musculoskeletal disease present	-0.06	0.59
Comorbid cardiovascular disease present	-0.10	0.37
Comorbid mental disease present	-0.29	0.01*

Additional effects on course of SBP (Panel B):

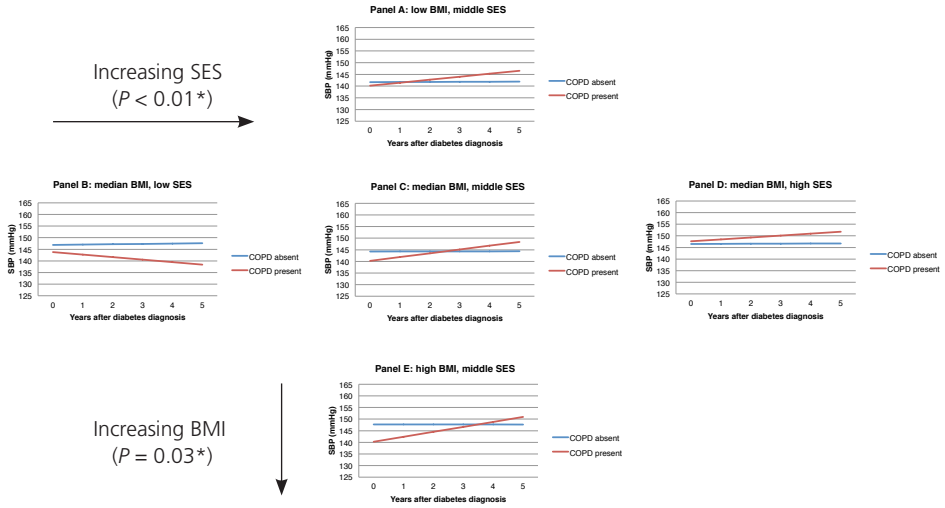
Variable	Effect on SBP (mmHg)	*P*-value
Female sex	+2.0	0.11
Middle SES	-2.5	0.14
High SES	-0.02	
Low BMI	-2.3	<0.01*
High BMI	+3.2	
Young age	-4.0	<0.01*
Old age	+4.0	
Comorbid malignancy present	-4.1	0.11
Comorbid musculoskeletal disease present	-0.3	0.83
Comorbid cardiovascular disease present	+4.3	<0.01*
Comorbid mental disease present	-3.5	0.02*

FIGURE 2: Mixed model results (no subgroup effect analysis)

Longitudinal HbA1c (A) and SBP (B) outcomes of diabetes patients with and without comorbid COPD. Comorbid diseases: absence and presence are assessed on the date of diabetes diagnosis. Number (n) of cases with completed longitudinal analysis (no missing data on any of the variables included in the mixed model throughout): 582. Cases with missing values for BMI: n = 23, cases with missing values for SES: n = 5. **P*-values < 0.05. Age and BMI categories: based on the distribution of age and BMI values of patients contributing to the analyses, limits for 'low', 'intermediate' and 'high' values were 54, 64 and 72 years for age, and 26.0, 28.5 and 31.8 kg/m^2 for BMI, respectively. Graphs for 'reference categories': in the graphic presentation, graph lines represent HbA1c or SBP courses for specific patient variables - for example, a male patient from the low-SES group with a specific age and BMI. We define the (theoretical) combination of the patient characteristics 'male sex, low SES, median age, median BMI and absence of other comorbidity' as 'reference category'. The 'Additional effects table' below each graph contains information needed to construct lines of predicted outcomes, based on the mixed model results, for other subjects than the 'reference category'. It shows the additional effects (to be added to the graphs displayed above) for other covariates included in the model. These values are not time dependent and not dependent on the absence or presence of COPD. Example: HbA1c courses over time for patients with and without comorbid COPD are shown in A. The 'Additional effects table' shows an additional effect of +0.04 (% HbA1c) for female sex. This means 0.04 should be added to the blue line for female patients without COPD and 0.04 should be added to the red line for female patients with COPD. The *P*-value of 0.70 shows that this additional effect of sex on HbA1c in this analysis is not statistically significant. BMI, body mass index; COPD, chronic obstructive pulmonary disease; SBP, systolic blood pressure; SES, socioeconomic status.

In the subgroup effect analyses, however, we found a statistically significant association between comorbid COPD and the course of SBP, with effect modification of SES ($P < 0.01$) and BMI ($P = 0.03$). To express these complex findings in a comprehensible way, Figure 3 shows a graphical representation of the direction of effects, with separate graphs for combinations of SES and BMI. The Figure shows that in the absence of COPD (blue lines), longitudinal SBP values are relatively stable over time, with higher values

when BMI is higher (compare Panels A, C, and E). Diabetes patients with comorbid COPD (red lines) showed a more variable course of SBP over time, with SES more than BMI defining the direction of effects and absolute SBP values. Note that, in the subgroup effect analysis, nonsignificant terms were removed from the model; i.e., all variables presented contributed significantly to the model predicting the outcome. Age ($P < 0.01$), presence of comorbid mental ($P = 0.03$) and comorbid cardiovascular disease ($P < 0.01$) had additional effects on the subgroup effect analysis results (not dependent on the presence or absence of comorbid COPD, additional effects). Absolute values depended on the mix of patient characteristics. No significant effect modification was found from any of the defined subgroups on the longitudinal development of HbA1c in the presence of comorbid COPD.



Additional effects on course of SBP (all Panels):

Variable	Effect on SBP (mmHg)	*P*-value
Young age	-4.0	<0.01*
Old age	+4.0	
Comorbid cardiovascular disease present	+4.1	<0.01*
Comorbid mental disease present	-3.2	0.03*

FIGURE 3: Mixed model results for subgroup effect analysis

5-year course of SBP for diabetes patients with and without comorbid COPD, modified by SES ($P < 0.01$) and BMI ($P = 0.03$). The explanations are the same as Figure 2. Graphs are shown for the 'reference category' (i.e., male sex, median age, absence of other comorbidity), but SES and BMI vary as specified in the figure. BMI, body mass index; COPD, chronic obstructive pulmonary disease; SBP, systolic blood pressure; SES, socioeconomic status.

Sensitivity analysis

After exclusion of cases with incident COPD during the 5-year follow-up period, we did not observe a significantly different association between COPD and HbA1c ($P = 0.54$) or SBP ($P = 0.34$), nor did we observe significant differences in the results from the subgroup effect analyses.

DISCUSSION

Main findings

In the current study, we explored the association between comorbid COPD and the longitudinal development of HbA1c and SBP in a representative cohort of newly diagnosed type 2 diabetes patients in primary care during 5 years of follow-up. The initial analyses showed no significant associations between COPD and these outcomes, but subgroup effect analysis indicated that, in the presence of COPD, the development of SBP was different for patients from different SES and BMI subgroups. This suggests that comorbid COPD, in relation with these particular patient characteristics, may influence long-term diabetes control parameters.

STRENGTHS AND LIMITATIONS OF THIS STUDY

In this dynamic cohort study, we used data from robust datasets that originate from decades of experience in morbidity recording in a practice-based research network from our department[20] and good quality of diabetes care.[22] We studied relevant diabetes control parameters as study outcomes (not 'treatment intensification'[27,28]) over a follow-up period that was long enough to assess potential associations with comorbid COPD. Comparison of outcomes over time between patients was meaningful, as we included only newly diagnosed diabetes patients. Another strength is that we studied an unselected population with 'real patients' receiving regular primary health care, i.e., a representative sample of the type 2 diabetes patient population.

It is important to realise that, within our study period, the criteria for the diagnosis of COPD and diabetes have changed. The current criteria for diagnosing COPD were introduced in Dutch general practice in 2001.[29] Towards the end of our observation period, there was a higher rate of diabetes diagnoses.[30] This implies that COPD and diabetes data from early in the observation period may not be fully comparable to similar data at the end of the period. This type of limitation is inherent to working with longitudinal data. In general, the CMR has shown to record diagnoses with high validity.[31]

One limitation of this study is that we were unable to account for smoking in the analyses, because this has not been consistently recorded in the CMR and NMP databases, nor

did we have data available on the severity of COPD (i.e., degree of airflow obstruction, exacerbation rate, severity of dyspnoea). From a previous study, we know that the majority of COPD patients in the NMP registry have mild or moderate COPD,[25] but from our current work we cannot tell whether and how the severity of underlying COPD may be associated with the course of diabetes outcomes.

Clearly, the development of HbA1c and SBP over time as observed will have been influenced by the diabetes treatment as provided by GPs. This treatment may include stimulation of physical exercise (which is beneficial not only for the diabetes but also for the COPD) and prescription of glucose-lowering medication.[32] Medication prescribed for COPD (e.g., oral or inhaled corticosteroids) may increase the glucose level and SBP in patients with diabetes.[33,34] In this dynamic cohort study, it was not possible to compare therapeutic regimes between diabetes patients with and without COPD. Differences in medication or lifestyle regimes may have contributed to the observed differences.

Twenty-eight cases with missing data for SES or BMI throughout the follow-up period (variables included in the linear model) dropped out. Their numbers were relatively low, which makes it unlikely that they introduced bias.

The percentage of diabetes patients with comorbid COPD in our cohort corresponds with prevalence numbers described in the literature.[9–11] Although the absolute number of patients with COPD (n = 63) was relatively low, one of the subgroup effect analyses did show significant results. In a larger sample of diabetes patients with comorbid COPD, it would have been possible that some nonsignificant trends observed would have reached statistical significance.

The current paper is one result of a larger project with an explorative design aimed at investigating associations between several types of comorbidities on diabetes control parameters. These results generate new hypotheses and may guide further research elaborating on the early findings. It helps increase the evidence base for the complex care to patients with multimorbidity. We believe that the most important strength of the current work is precisely this novelty. To the best of our knowledge, this is the first study exploring longitudinal associations between COPD and another common chronic disease, in this case diabetes. Because the combined occurrence of diabetes and COPD is common, assessing possible interactions in terms of long-term outcomes is important. Our observation that, in some subgroups, comorbid COPD was associated with altered diabetes outcomes warrants further research in this area. Our study may serve as an example of how to investigate the complex relationships between two or more chronic conditions (i.e., multimorbidity) on patients' prognoses for the diseases involved.

Interpretation of findings in relation to previously published work

The unfavourable effect of increasing BMI on systolic blood pressure is not surprising.[35] Our observations indicate that for diabetes patients with comorbid COPD, patient characteristics that predict long-term outcomes may be different from those without COPD. Our study design had an explorative nature in which we tested several associations; hence, care needs to be taken in the interpretation of our findings. We did not find significant associations between comorbid COPD and all study outcomes tested. It is possible that the significant associations between longitudinal SBP and comorbid COPD among diabetes patients may not be replicated in a future study. It cannot be concluded from observational research only whether and how our findings should be translated into therapeutic consequences. One could reason that, in patients with diabetes and comorbid COPD, factors related to a patient's SES are more important in achieving longterm SBP control than just reducing BMI. Our finding that among COPD patients the lower SES group had the best long-term SBP control is surprising, but this finding would first need to be confirmed in a larger study before we should speculate about possible explanations. In our cohort, diabetes patients with comorbid COPD had different (comorbidity) characteristics than those without COPD – an important notion for the treatment of patients with either or both of these diseases. The observed differences may result from disease-specific or from generic factors such as obesity, lifestyle and smoking. The need for more research aiming at profoundly investigating the associations between COPD, SES and diabetes control parameters is obvious. Previous studies described negative associations between low SES and COPD[36] and diabetes[19] prognosis. Studies reporting on the relationship between SES and prevalence of multimorbidity in general described negative associations.[37–39] We have not been able to trace any previously published papers paying attention to the role of SES in relation to the specific combination of COPD and diabetes.

After the first recognition of the importance of lipid regulation in diabetes,[40] the revised version of the Dutch College of General Practitioners diabetes guideline in 1999 resulted in increased attention to the role of lipids halfway through our study period. For this reason, and as studying one glycaemic and one nonglycaemic control parameter already resulted in a large data set with many associations tested, we decided not to include lipids as diabetes control parameters.

Some covariates showed significant additional effects, both on the nonsignificant results from the initial models and on the significant subgroup effect analysis results. Note that these are independent from time and from the presence/absence of COPD. Augmenting effects from increasing BMI and age (on both study outcomes) and from comorbid cardiovascular disease (on SBP) can be expected among diabetes patients. We assume that the consistent diminishing effect of comorbid mental diseases is related to

a higher consultation frequency among these patients,[41] offering more opportunities to diagnose and manage diabetes (or hypertension) in an early stage, resulting in slightly better outcomes.

Pathophysiologic mechanisms that have been suggested to have a role in the relationship between respiratory impairment in COPD patients and diabetes include an increased BMI, altered respiratory compliance, weakness of the respiratory muscles or neuropathies.[7]

GPs' beliefs about the feasibility and benefits of medication regimes may be influenced by the presence of comorbidity,[42–44] which might result in deliberate flexible medication prescriptions in patients with comorbidities. Given these considerations, we believe that the absence of an association between comorbid COPD and long-term HbA1c outcomes among diabetes patients implies that GPs responsible for treatment provide good-quality diabetes care despite the presence of comorbidities such as COPD.

Implications for future research, policy and practice

The current study provides novel observational data in a research area that is still underdeveloped, i.e., multimorbidity. It focuses on the impact of COPD as a comorbid disease in patients with diabetes. Comorbidity should be regarded as a patient characteristic that may influence relevant outcomes of another disease. Instead of focusing mainly on disease-specific outcomes, future research should pay more attention to the effects of comorbidity and other patient characteristics such as sociodemographic background. Moreover, future work may study the effects of (other) incident comorbidity on diabetes outcomes in more detail. Further investigations of potential associations between diabetes, and other prevalent chronic diseases, with relevant COPD outcomes are desired too, as well as other combinations of diseases.

The majority of practitioners caring for patients with either COPD or diabetes will see several patients with these diseases combined, and our findings may help raise awareness on the importance of formulating personalised management plans that aim for sensible outcomes taking into account both diseases. The current explorations do not yet allow for concrete recommendations for daily practice changes – our findings need to be replicated in larger diabetes cohorts.

Knowledge of the impact of comorbidity on disease outcomes is also important to support pay-for-performance initiatives that facilitate patient-centred care. Therefore, ongoing research in this area should be prioritised by funding bodies and policymakers.

Conclusions

Comorbid COPD was associated with longitudinal control parameters of newly diagnosed type 2 diabetes patients in general practice. This association was observed on SBP (but not on HbA1c) and was modified by SES and BMI. Although these results need to be verified first, this exploratory study provides new information on the interaction between multiple chronic diseases, and may guide further development of personalised care that accounts for patients' comorbidity.

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Chapter 5

GPs' considerations in multimorbidity management: a qualitative study

Hilde Luijks
Maartje Loeffen
Toine Lagro-Janssen
Chris van Weel
Peter Lucassen
Tjard Schermer

Br J Gen Pract 2012; **62**: e503-10

GPs' considerations in multimorbidity management: a qualitative study

ABSTRACT

Background

Scientific evidence on how to manage multimorbidity is limited, but GPs have extensive practical experience with multimorbidity management.

Aim

To explore GPs' considerations and main objectives in the management of multimorbidity and to explore factors influencing their management of multimorbidity.

Design and setting

Focus group study of Dutch GPs, with heterogeneity in characteristics such as sex, age and urbanisation.

Method

The moderator used an interview guide in conducting the interviews. Two researchers performed the analysis as an iterative process, based on verbatim transcripts and by applying the technique of constant comparative analysis. Data collection proceeded until saturation was reached.

Results

Five focus groups were conducted with 25 participating GPs. The main themes concerning multimorbidity management were individualisation, applying an integrated approach, medical considerations placed in perspective, and sharing decision making and responsibility. A personal patient–doctor relationship was considered a major factor positively influencing the management of multimorbidity. Mental health problems and interacting conditions were regarded as major barriers in this respect and participants experienced several practical problems. The concept of patient-centredness overarches the participants' main objectives.

Conclusion

GPs' main objective in multimorbidity management is applying a patient-centred approach. This approach is welcomed since it counteracts some potential pitfalls of multimorbidity. Further research should include a similar design in a different setting and should aim at developing best practice in multimorbidity management.

INTRODUCTION

Multimorbidity is described as 'the presence of multiple chronic conditions'.[1, 2] Definitions of multimorbidity and the related concept of comorbidity lack uniformity, which hinders comparability of results of clinical and epidemiologic studies.[3] Any prevalence estimate of multimorbidity heavily depends on the number of conditions considered and the population under study.[4-6] Estimates in adults in general practice or population-based settings that are not confined to older age groups vary from 16 to 58%,[4, 7-9] with outliers up to 90%.[10]

With increasing numbers of medical conditions within one patient, hospital admission rates and healthcare expenditures raise dramatically.[11] Patients with multimorbidity account for most consultations in primary care:[4] they present more intercurrent morbidity in doctor visits than patients with single diseases,[12] and GPs deal with the majority of these 'additional' patient visits.[13]

For patients, multimorbidity has negative consequences in terms of quality of life as well as mortality.[14-16] In recent years, a number of qualitative studies have been published, focusing on patients' views of and experiences with multimorbidity. Specific aspects arising from these studies were problems with medication and management,[17-20] interaction of one condition with another,[17] difficulty in perceiving and recognising symptoms,[20] and problems with logistics or organisation of care.[21]

Studies of healthcare professionals' experiences and management of multimorbidity reported lack of time for appropriate management and organisational and logistical challenges, but included small numbers of practitioners.[22-24] Decisions on patients with multimorbidity demand a focus exceeding the single disease level. This makes it relevant to explore in depth the decision-making process among physicians. Managing multimorbidity is daily practice for most GPs, even though evidence and guidance is limited.[1-3, 25] As a consequence, GPs' experiences might provide useful insights for coping with patients with multimorbidity.

This qualitative study explored GPs' considerations and main aims in the management of multimorbidity. The secondary objective was to explore factors influencing this management in daily practice.

METHOD

Study design and participants

Focus group interviews with Dutch GPs were carried out. In the Netherlands, all patients are enlisted with a GP, who on average deals with more than 95% of presented medical problems[26] and arranges referral to secondary care when needed. For those who receive specialist care, the GP remains involved in their health care.

Participants were recruited among GPs working within 40 miles of Nijmegen, in the eastern part of the Netherlands, through mail and telephone contact. A purposive sampling strategy was applied to ensure heterogeneity in characteristics such as age, sex, and urbanisation among the participants. Stepwise sampling was performed,[27] as in qualitative research, sampling, data collection and analysis typically occur in an iterative process. Academic involvement was recognised as characteristic, possibly influencing a participant's beliefs concerning the research question and led to sampling of participants with and without involvement of research or training in the GP residency programme.
As it was expected that GPs would contribute substantially to the discussion due to familiarity with the topic, the number of participants in each focus group was kept relatively low (four to six), thereby allowing all GPs to express their ideas. The groups were large enough to potentiate discussion and produce new insight. All GPs consented to participate and anonymity and confidentiality were ensured. Participants were offered a gift voucher and compensation of travel expenses in appreciation of their efforts. Interviewing healthcare professionals with respect to professional beliefs does not require approval of an ethics committee according to Dutch legislation.

Focus group interviews and data collection

Moderator of the focus groups was a GP-senior researcher with extensive experience in qualitative research and in moderating focus groups. An interview guide was used to cover items addressing the research question. (Further details are available from the author). Its construction was based on discussions in the research team and a test session with junior researchers and residents in the university department. Member checking to improve validity was performed informally during focus group sessions.[28]
One researcher observed all groups and made field notes of non-verbal communication. The interviews lasted 75–90 minutes.
All group interviews were audiotaped and transcribed verbatim by a medical student. The observer checked the transcripts during tape listening and corrected these when necessary.

Analysis

Analysis was performed using the technique of constant comparative analysis.[29] Two data analysts first familiarised themselves with the data, and subsequently applied open coding, hereby conceptualising the data. Codes were tabulated and connected in the axial coding phase. Selective coding was used at the highest level of abstraction, in which the core variable guided further relevant coding, and the data were sought for invalidating examples.
The two analysts discussed the initial coding and consulted a senior researcher in case of disagreement. Interpretation of the main theme was discussed in the entire research

team. Data collection proceeded until saturation was reached, meaning that no new major themes arose from analysis. This was the case after the fifth focus group meeting. Analysis processing was supported by Atlas.ti software.

The methods applied were appropriate in light of the philosophical paradigm 'realism' we feel most aligned with.[28] This paradigm fits the authors' backgrounds as primary care physicians and as participants of quantitative as well as qualitative research.

RESULTS

Participants

Five focus group interviews were conducted between September 2010 and March 2011 with 25 GPs, with a mean age of 50 years. Characteristics of the participants are presented in Table 1. Sufficient heterogeneity in their characteristics was reached.

TABLE 1: Characteristics of participating GPs[1]

	n (%)
Sex	
Male	18 (72)
Female	7 (28)
Practice type	
Single[2]	4 (16)
Duo or group	21 (84)
Urbanisation	
Rural area	2 (8)
Urbanised rural area	16 (64)
Urban area	7 (28)
GP trainer[3]	
At present	11 (44)
In the past	1 (4)
Never	13 (52)
Researcher	
Yes	5 (20)
No	20 (80)
Mean age, years (range)	50 (31-63)
Mean experience as GP, years (range)	20 (2-36)

[1]Sex, age, practice type and urbanisation were similarly distributed among participants in our sample as compared to the Dutch professional group of GPs.[26]

[2]Count of GPs settled solitary in a practice, i.e. without employment of, or professional collaboration with other GPs.

[3]Trainer at the Nijmegen residency training programme, a qualification needed to supervise a GP trainee.

Overview of results

The main themes in the management of multimorbidity were individualisation, applying an integrated approach, medical considerations placed in perspective, and sharing decision making and responsibility. A personal patient-doctor relationship was considered a major facilitator in the management of multimorbidity. Presence of mental health problems was regarded as complicating factor. Participants also experienced difficulties resulting from conditions interacting with each other and several practical problems. Overarching concept of the main findings is patient-centredness.

Group discussions were focused on older and disabled people. The results are classified in two sections, 'management of multimorbidity' and 'influencing factors', and discussed in more detail below.

Management of multimorbidity

Individualisation

This theme was discussed at length in each focus group and reappeared in discussions on other themes. GPs agreed on the need to adapt management of multimorbidity to personal circumstances of these patients, such as vitality, personal preferences (for example retaining independence as the ultimate goal) and socioeconomic conditions. They stressed the importance of tailoring care to the individual and tried to understand the meaning of illness for a person:

> *'There are people that take lots of risks in their lives and there are people that are very careful. I think that tendency carries over in medical decision-making.'* (GP7, male, 56 years)

> *'From a medical perspective, I'd say don't bother, eh, with hemiparesis and, uh, but he wanted to, and I know why. It's because his wife has dementia and he's her [caregiver].'* (GP19, female, 52 years, talking about resuscitation)

Integrated approach

GPs often stated that adhering to standard regimens or strict guidelines was unwanted, as it contradicts their integrated perception of a unique person with a specific combination of diseases. Particularly in multimorbidity, fragmentation of care is a pitfall. GPs perceived a disease-centred approach as insufficient, because multiple conditions and corresponding advices need integration and coordination. Many perceived a coordinating role appropriate for GPs:

> *'[Patients have] the sense that they're a collection of organs and, uh, there's someone that does some work on one part and someone else that does work on another part, and the whole, yeah, that's your job as a GP, to keep an eye on the whole of the parts.'* (GP1, female, 36 years)

> *'Precisely when there is multimorbidity, we as GPs have a role of increasing importance. So I think we all need to take responsibility here, and should not have the specialist responsible. […] I am the one who draws up the balance, because in the hospital, there is no generalist.'* (GP7, male, 56 years)

Participants brought up the need for a generalist approach in multimorbidity and explained how they attempted to achieve this. The total burden of diseases and other relevant problems were taken into account when patients present single diseases:

> *'You can't just quickly check for diabetes. That's a useless endeavor as far as I'm concerned, because, in the meantime, there's the gout and the arthritis and this and that. And you need to take that into account as well.'* (GP13, male, 45 years)

Medical considerations placed in perspective

It was noted that, in patients with multimorbidity, other considerations can become complementary or even superior to medical motives, although, unsurprisingly, multimorbidity management is primarily based on medical motives. Patients' quality of life was the main focus of GPs' professional performance. However, converting this aim into appropriate medical practice was a struggle for many GPs. They incorporated patients' life-expectancy and age in medical decisions. Many GPs shifted their focus towards present comfort if prognosis was limited. In such cases, most GPs chose symptom relief over causal treatment:

> *'When you are dealing with multiple conditions […] there's increasingly more disability as the end of one's life nears, so to speak. You then approach things differently, eh. All the medical stuff becomes relative. And reaching targets becomes less important and checking stats, and crossing the Ts and dotting the Is […] becomes less important.'* (GP13, male, 45 years)

In all groups, the search for a balance between the patient's 'disease' and 'illness' was expressed in different wordings:

> *'That's difficult. See, it's always a matter of finding a balance between what the patient wants, the burden of the treatment for him, and the potential good you think it will do. And what does the patient experience as good?'* (GP24, male, 56 years)

Sharing decision making and responsibility

GPs agreed that they want to involve their patients' perspectives and preferences into the decision-making process. Exploring and mutually explaining ideally resulted in 'shared decision making':

> *'I don't want anything, he said […] and, even then, you need to explain exactly what it is he's opting for and then you can, in my opinion, even with very elderly people, you can jointly decide on things.'* (GP7, male, 56 years)

Involvement of patients and other caregivers implied that not only decisions, but also responsibilities, are shared. In general, GPs expressed a broad sense of responsibility:

> *'Well, I think it pretty much means that I provide care to that patient and that I get an update every year and half on how his organs are doing. But I feel responsible for him.'* (GP7, male, 56 years)

> *'I do indeed think that it's simply our job to, uh, try to keep tabs on things - maintain an overview - and provide information and then check things, and to let the patient think with you, that is, if you think that's realistic.'* (GP5, female, 33 years)

Most GPs agreed that shared responsibility implies that different viewpoints of doctor and patient should be anticipated:

> *'You see, if someone repeatedly says, sure, nice idea doctor, and I know what it all means but it's not for me, then, then I will, in time, support that patient's choice.'* (GP14, male, 63 years)

They expressed variation in the responsibilities allocated to themselves when care provision to patients with multimorbidity was shared with medical specialists. GPs who felt comfortable with disease-management to be primarily arranged by specialists for 'independent' patients, tended to act more as coordinator when a patient was more 'care dependent'.

Influencing factors

Personal relationship

Over time, Dutch GPs build a longstanding, rather personal relationship with most patients, certainly in the case of multimorbidity:

> *'But the fact that you've known the patient for a long time by then obviously makes a difference.'* (GP12, female, 58 years)

This was considered to facilitate multimorbidity management, with continuity of care as an elementary component. Apart from explicit comments GPs made on its importance, the personal relationship between GP and patient could be noticed implicitly from comments on personal events of patients:

> *'I think that you need to gain the trust of the patient, and that trust can be gained, I think, by showing interest, eh, by talking with them about the social context.'* (GP14, male, 63 years)

> *'We see how they interact with their children. We see how they interact with their neighbours. We sometimes have a much, uh, broader view.'* (GP2, male, 60 years)

> *'Yeah, but this is my bicycle repairman […] It's Harry!'* (GP5, female, 33 years)

Mental health problems

Most participants mentioned that a co-existing psychiatric disorder substantially complicated their management of chronic somatic illnesses. Diagnostics are hindered ('overshadowed') because these patients show a different symptom presentation. Moreover, GPs regarded patients with medically unexplained symptoms as another difficult group in the case of multimorbidity. Although precisely the presence of multimorbidity raised appreciation, patients suffering from anxiety about having various diseases seemed to be considered as more bothersome by some GPs. Furthermore, cognitive impairment of patients with multimorbidity heavily impedes the management as it results in limited feasibility of adherence to treatment regimens:

> *'They come back another time with somatisation …-like complaints. And then I start to find it awfully complicated.'* (GP2, male, 60 years)

> *'You have [older people] who have 10 different health complaints, but they sit down and it's clear they have one new problem — this and that is wrong with me. But chronically depressed patients, they come in and they tell you that but they also tell you about 10 other complaints, this is bothering me and could you just take a look at this […] That always makes it more difficult to consider new explanations for the complaints.'* (GP24,male, 56 years)

Interacting conditions

Interaction of several conditions when patients have multimorbidity resulted in difficulties in diagnostics as well as in therapeutics. Assignment to which condition specific symptoms should be attributed to could be difficult:

> *'Often their complaints cannot easily be traced back to one single condition.'* (GP6, female, 31 years)

> *'What does this fit with? Which condition? […] He had intestinal ischemia of the mesenteric artery, and then he had abdominal pain so he came back with abdominal complaints, but he also has IBS [irritable bowel syndrome].'* (GP23, male, 51 years)

Some GPs described that an explanation is sought within known conditions and the option of an additional disease is easily overlooked. At a therapeutic level, multiple conditions might demand conflicting approaches, such as steroid administration to patients with diabetes:

> *'I have someone […] whereby it's clear that what helps one complaint harms another.'* (GP5, female, 33 years)

Another problem could be appropriate problem registration in the patient's medical record.

Practical problems

GPs experienced several practical aspects as impeding multimorbidity management. In general, they felt there was insufficient time and compensation for consistently putting into practice their main objectives. Polypharmacy, considered a distinct issue associated with multimorbidity, was experienced by most as potentially harmful yet hard to reduce. Moreover, coordination and overview on medication were hard to maintain. Importance of the GP being well informed on a patient's current medication was stressed:

'To me, it's often difficult to ehh, maintain an overview. These patients see quite a number of different specialists, and to me it seems that one specialist still doesn't know what the other ones are doing.' (GP23, male, 51 years)

DISCUSSION

Summary

This study explored GPs' considerations and main aims in managing multimorbidity. These were individualisation, applying an integrated approach, medical considerations placed in perspective, and sharing decision making and responsibility. A personal patient–doctor relationship was considered beneficial. Major impediments in multimorbidity management, besides some practical problems, were mental health problems and interacting conditions. The main considerations of GPs perfectly fit in the concept of patient-centredness. The GPs in this study considered this as most important when managing patients with multimorbidity.

Strengths and limitations

The study sample has a high percentage of academically-engaged GPs but there were no important differences in opinions with GPs without academic involvement. Although qualitative research does not allow for generalisations, this sample's resemblance to the Dutch GPs' professional group improves the transferability of the study's findings.[26, 27]

With this qualitative approach GPs' considerations and main aims in multimorbidity management were explored. Conclusions cannot be drawn regarding actual behaviour; however, assessment of behaviour fell outside the scope of this study.

Rigorous qualitative methods were applied. A focus group study was considered to be an appropriate qualitative approach, since opposing perspectives could lead to a deeper exploration of GPs' attitudes and experiences.[30] Data collection continued until saturation was reached, as prescribed in qualitative methodology.

Focus groups were conducted in the Dutch language. Illustration of representative quotations needed translation, which may have caused loss of some refining. This effect was reduced as much as possible as the translation was performed by a native English speaker who works as a healthcare scientist.

To the authors' knowledge, this is the first qualitative research paper focusing on multimorbidity from the perspective of primary care physicians specifically. An important and new finding was their strong emphasis on patient-centredness. In the authors' opinion, this novelty is the major strength of this study.

Comparison with existing literature

Several conceptual models of patient-centredness in primary care exist.[31, 32] Common factors in these models are 'regarding the patient as whole person', 'attention to both disease and illness', 'sharing power and responsibility' and a 'personal doctor-patient relationship'.[33] This last factor came up as facilitator to multimorbidity management in the current study. The considerations 'individualisation' and 'integrated approach' can jointly be regarded as matching 'regarding the patient as whole person', since they emphasise to apply a holistic, personalised approach. 'Medical considerations placed in perspective' corresponds with 'attention to both disease and illness' because both stress that the biomedical model needs to be complemented with the patient's perspective. 'Sharing decision making and responsibility' matches 'sharing power and responsibility'. This study's findings can serve as examples showing that the participating Dutch GPs considered a patient-centred approach most important in their care for patients with multimorbidity.

The main barriers identified in multimorbidity management were associated with the complexity of diagnosis (interaction, mental health problems) and treatment (polypharmacy and interaction). From the viewpoint of patient-centredness, these can be perceived as compromising the achievement of shared decision making and the application of an integrated approach. It is possible that achieving 'integration' is more challenging as the number of dimensions that need to be integrated (such as, biomedical, psychological, and socioeconomic), increases. Ideally, clinicians display patient-centredness persistently, but the need to rely on it may grow with increasing complexity, for instance in multimorbidity. This idea is supported by the finding that professionals' management of multimorbidity in heavily deprived areas has an even stronger emphasis on the 'whole person', seeming to overrule biomedical considerations completely.[34] Other work showed that realising concurrent effective management of somatic and mental conditions is hard.[35] Kendrick *et al.* have shown that patients with depressive symptoms with comorbidity were less likely to receive prescriptions or referral than those without comorbidity, accentuating the complex relationship between coexisting somatic and mental illness.[36]

Multimorbidity comes along with potential pitfalls, such as opposing treatment strategies and fragmentation of care, stimulated by disease-centred reimbursement systems, and it challenges our capacities for organisation of care including recording of clinical information; therefore patient-centredness is warranted.[1, 37-43] Patient-centredness can be regarded as 'tool' to counteract multimorbidity's potential pitfalls. It could be perceived as intuitively appropriate and thus a common sense result. However, it is an important finding that has not arisen from earlier studies. GPs, supported by a personal relationship with the patient, are the healthcare professionals with an excellent background to put

patient-centredness into practice. They have broad generalist knowledge, enabling them to balance patient level consequences from several conditions. Interaction of multiple diseases and medications demands integrated care with someone watching over it being coordinated. Who else than the familiar and accessible GP should be more suited to play this role? It would demand the flexibility to focus on general and patient level formulated outcomes, instead of disease-specific outcomes. Awareness can be raised and skills improved by paying attention to multimorbidity in training to both pre- and postgraduates.

This study sampled only GPs while previous studies also included nurses and pharmacists.[22-24] As a consequence, the current study allowed an in-depth focus on GPs' considerations in multimorbidity management. Originating from a specific professional perspective and educational background, doctors, nurses and other professionals might well display different considerations and objectives in their care for patients with multimorbidity. This reasoning is supported by different accents displayed in GPs' and practice nurses' visions on multimorbidity.[34] An in-depth identification of the considerations and perceived barriers and facilitators from specific professional groups separately could be considered a first step towards optimal integration of each group's specific knowledge and skills.

Earlier qualitative work identified expressions of uncertainty by professionals about their ability to manage the complexities following from multimorbidity.[23] Although this study located certain similar remarks, it also identified opinions stressing that GPs are appropriate professionals to deal with multimorbidity due to their generalist approach, and should be considered as experts in this regard.

Perceived barriers to multimorbidity management in this study, contrasting with the earlier studies, were not confined for the greater part to practical consequences such as workload or inconvenience, but extended to the more conceptual level of multimorbidity and included diagnostic and therapeutic complexities.[22–24] Some of these differences with other studies may be related to differences in the sample of healthcare professionals, or to differences in the extensiveness of the qualitative approach. Furthermore, it might be the case that the UK, with the Quality and Outcomes Framework, as well as the US have a stronger emphasis on adherence to disease-oriented guidelines than the Netherlands. Doctors may perceive fewer options to display or prioritise patient-centredness as this tendency increases. It urges us to assess which treatment strategies are effective and efficient for patients with multimorbidity specifically.

Implications for future research

The current findings show that GPs' main objective in multimorbidity management is patient-centredness. Since such an approach seems appropriate, but has not arisen

earlier, it should be investigated whether a similar study design in a different setting would result in similar findings. It is not yet known to what extent these findings are related to specific primary care professions, such as GPs, or the (Dutch) primary care context. Furthermore, investigating professionals' actual behaviour in multimorbidity management is among the main points of action to be employed in the nearby future. The current findings can serve as a starting point in this respect.
It is time to evolve expertise and develop best practice in multimorbidity management. Generalists in primary care are perfectly suited to start such a movement.

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Chapter 6

How GPs value guidelines applied to patients with multimorbidity: a qualitative study

Hilde Luijks
Peter Lucassen
Chris van Weel
Maartje Loeffen
Toine Lagro-Janssen
Tjard Schermer

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How GPs value guidelines applied to patients with multimorbidity – a qualitative study

ABSTRACT

Aims

To explore and describe the value GPs attribute to medical guidelines when applied to patients with multimorbidity, and to describe which benefits GPs experience from guideline adherence in these patients. Also we aimed to identify limitations from guideline adherence in patients with multimorbidity, as perceived by GPs, and to describe their empirical solutions to manage these obstacles.

Design

Focus group study with purposive sampling of participants. Focus groups were guided by an experienced moderator, who used an interview guide. Interviews were transcribed verbatim. Data analysis was performed by two researchers using the constant comparison analysis technique and field notes were used in the analysis. Data collection proceeded until saturation was reached.

Participants

Dutch GPs, heterogeneous in age, sex and academic involvement.

Results

25 GPs participated in five focus groups. GPs valued the guidance that guidelines provide, but experienced shortcomings when applied to patients with multimorbidity. Taking these patients' personal circumstances into account was regarded as important, but impeded by a consistent focus on guideline adherence. Preventative measures were considered less appropriate in (elderly) patients with multimorbidity. Moreover, the applicability of guidelines for patients with multimorbidity was questioned. GPs' extensive practical experience with managing multimorbidity resulted in several empirical solutions, for example using their 'common sense' to respond to the perceived shortcomings.

Conclusions

GPs applying guidelines for patients with multimorbidity integrate patient-specific factors in their medical decisions, aiming for patient-centred solutions. Such integration of clinical experience and best evidence is required to practice evidence-based medicine. More flexibility in pay-for-performance systems is needed to validate this integration. Several improvements in guideline reporting are necessary to enhance guidelines' applicability to patients with multimorbidity.

INTRODUCTION

Multimorbidity, the existence of multiple chronic conditions within a particular patient,[1] is very common.[2-5] It has a substantial impact on health care utilisation and costs[5-7] and on patient outcomes,[7, 8] putting great demands on global health care. Care for patients with multimorbidity is complex, requiring coordinated care, management of chronic diseases and medication, which may be challenging for practitioners having only short consultations available.[9]

Evidence-based medicine and guidelines have improved the quality of healthcare through better diagnostic and therapeutic treatment decisions. But their application can be problematic when a patient has more than one disease, as guidelines are generally written for single diseases, with limited suitability for multimorbidity.[10-12] A focus on single disease guidelines brings the risk of 'siloing of care' for patients with multimorbidity.[13, 14] NICE is preparing a guideline on the clinical assessment and management of multimorbidity.[15] The wide spectrum of multimorbidity is a practical limitation to develop guidelines for disease combinations. However, guidance in how to combine or prioritise guideline recommendations or when to stop recommended treatments could improve the care for patients with multimorbidity, but is missing in current guidelines.[14, 16, 17]

Given the high prevalence of multimorbidity, all clinicians may struggle with guideline application in patients with multimorbidity. Generalists however, who provide care to patients with any disease type without prioritising one disease over another beforehand, may specifically have well-formulated ideas on this issue. It is to be expected that GPs would have extensive experience in managing multimorbidity despite a gap in evidence-based guidance, and have developed practical solutions to deal with this gap. Many papers investigating practitioners' experiences with multimorbidity management however had a focus on the challenges they faced in the care for patients with multimorbidity, and not on their experiences with or solutions for handling guidelines in these patients.[18]

In the Netherlands, the Dutch College of General Practitioners (DCGP; *Nederlands Huisartsen Genootschap* (NHG)) has produced evidence-based guidelines covering 70-80% of the conditions presented in primary care. GPs play a leading role in the development and critical appraisal of these guidelines, of which 92 are currently available, and of which approximately one third concerns (potentially) chronic conditions.[19] DCGP guidelines cover diseases, complaints, and risk factors, and are established in a team composed of GPs, both with and without specific expertise concerning the topic, and representatives of other professional groups. Dutch GPs receive capitation payment, and with a limited additional payment for the management of chronic diseases such as diabetes and COPD when quality indicators are met. The Dutch College of GPs' guidelines are a main source of reference of diagnostic and therapeutic quality indicators.

Our objective was to explore and describe the value GPs attribute to medical guidelines

when applied to patients with multimorbidity, and to describe which benefits GPs experience from guideline adherence in these patients. Also we aimed to identify limitations from guideline adherence in patients with multimorbidity, as perceived by GPs, and to describe their empirical solutions to manage these obstacles.

METHOD

Study design and participants

As part of a larger research project on multimorbidity, focus group interviews with GPs have been held to explore GPs' aims and priority setting in the care they deliver to patients with multimorbidity, and the factors that facilitate and impede this.
We found that their main aim was to apply a patient-centred approach.[20] It was anticipated that the role of guidelines as potential facilitator or barrier of the care delivery to patients with multimorbidity might be mentioned. In the iterative qualitative process, in which data collection and analysis alternate, the insight grew that discussions on the role of guidelines, applied to patients with multimorbidity, provided important information meriting deeper exploration on itself. This resulted in formulating the current, additional research question: exploring the value GPs attribute to guidelines for multimorbidity. This topic came up spontaneously in the first focus groups and it was probed in the following group interviews if it did not arise spontaneously again. The original interview guide was not altered. When the role of guidelines had not yet been discussed spontaneously after discussing which factors were perceived as impeding factors in the management of multimorbidity, participants were asked if they perceived guidelines as an impeding, or as a facilitating factor in this respect. A separate qualitative analysis was performed on the same qualitative data considering the current research question. In a purposive sampling strategy, GPs from the academic network of the Radboud university medical center and from the personal network of the research team members were invited to participate, 'to gain more insight into GPs' experiences with the care for patients with multimorbidity'. They were contacted by mail and telephone. The location of their practices covered a 40 miles area around the city Nijmegen, in the eastern part of the Netherlands. Heterogeneity in characteristics such as age, sex, academic involvement and urbanisation was ensured. After having conducted four focus groups, in all of which at least one GP with an academic affiliation (GP trainer or researcher) participated, we decided to organise a fifth focus group with only non-academic GPs, since we anticipated that an academic affiliation might influence their ideas regarding the initial and the current research question. All GPs consented to participate. Anonymity and confidentiality were ensured. According to Dutch legislation, interviewing healthcare professionals regarding their professional beliefs does not need approval of an external

ethics committee. Participants were offered a gift voucher and compensation of travel expenses in appreciation of their efforts.

The focus groups were held between September 2010 and March 2011 and took place at the Radboud university medical center. One focus group was conducted in the practice of a research team member since this resulted in a shorter travel distance for the participating GPs. 25 GPs participated in five focus groups, each group containing four to six participants. Table 1 shows their characteristics. Some participating GPs knew the moderator, the observer, or other participating GPs in their focus group, whereas others didn't.

Focus groups can be regarded as appropriate qualitative methods, since the group process may help to explore and clarify views of participants, and facilitates different forms of communication, which could help in generating new insights.[21]

TABLE 1: Characteristics of participating GPs[1]

	n (%)
Sex	
Male	18 (72)
Female	7 (28)
Practice type	
Single[2]	4 (16)
Duo or group	21 (84)
Urbanisation	
Rural area	2 (8)
Urbanised rural area	16 (64)
Urban area	7 (28)
GP trainer[3]	
At present	11 (44)
In the past	1 (4)
Never	13 (52)
Researcher	
Yes	5 (20)
No	20 (80)
Mean age, years (range)	50 (31-63)
Mean experience as GP, years (range)	20 (2-36)

[1]Sex, age, practice type and urbanisation were similarly distributed among participants in our sample as compared to the Dutch professional group of GPs.[24]

[2]Count of GPs settled solitary in a practice, i.e. without employment of, or professional collaboration with other GPs.

[3]Trainer at the Nijmegen residency training programme, a qualification needed to supervise a GP trainee.

Focus group interviews and data collection

A GP-senior researcher with extensive experience in qualitative research moderated the focus groups, using an interview guide (available from the authors upon request). One researcher observed all group interviews and paid special attention to non-verbal communication. The observer's field notes were used during analysis, for example to identify non-verbally expressed (dis)agreement to other comments. The interviews were audiotaped and transcribed verbatim by a medical student.

Analysis

The constant comparative analysis technique was applied by two researchers to analyse the data for the current aims.[22] Disagreement was resolved by discussion or consultation of other researchers. The transcripts were read intensively. Open coding was first applied to conceptualise the data. This was followed by axial coding, where codes were clustered, side issues were distinguished from essentials, and initial concepts were checked against newly collected data. Selective coding was applied in the final analysis stage to integrate data after initial fragmentation. Invalidating examples were sought for. Data collection proceeded until saturation was reached concerning the current research question, which was the case after the fifth focus group. At this stage, no new insights were gained regarding GPs' evaluation of guidelines applied to patients with multimorbidity. ATLAS.ti (version 7, Berlin, Germany) supported the analysis. Citations illustrating important points discussed needed translation, which was performed by a native English speaker translator, familiar with qualitative research in healthcare. In this way, potential loss of refinement in translated citations was reduced as much as possible.

RESULTS

Overview of the results

GPs commented on the value of guidelines they perceived when applied to patients with multimorbidity, and on benefits from guideline adherence. They also described potential limitations from guideline adherence in these patients, which have led to several empirical solutions to counteract these. A point-by-point description of these discussed items is outlined below.

Value of guidelines applied to patients with multimorbidity

GPs valued evidence-based guidelines in general, and felt that their wide implementation had brought clear improvements to the quality of general practice. They especially perceived guidelines useful in the case of younger, relatively healthy patients, particularly if they suffered just from the disease described in the guideline. Most GPs followed

guidelines also for the younger and 'healthier' patients with multimorbidity, particularly if their multiple diseases had similar therapeutic approaches. In these cases of multimorbidity, guidelines provided guidance to medical decision-making, for example prescription of medication.

> *'If someone like that has COPD, then I think the guideline is very welcome and the same applies for the diabetes guideline.'* (GP24, male, 56 years)

> *'The DCGP guidelines are of course the standard that you can keep to as much as possible.'* (GP16, female, 44 years)[1]

Reduction of patients' perceived symptoms and complaints (pain, shortness of breath) was an important reason for GPs to adhere to guidelines in patients with multimorbidity.

> *'And of course, you go for the things that people really suffer from. Strict diabetes control…these days, that's not the main aim.'* (GP7, male, 56 years)

> *'Look, there are two things: prescribing something because of complaints, or to prevent something that will happen, or may happen in the future; that makes a big difference.'* (GP 24, male, 56 years)

Guideline adherence also helped in working transparently, enabling comparison and quality control between GPs. GPs did express a need for guidelines despite the difficulties in translating these into the practical care for patients with multimorbidity.

> *'Sometimes that should be left […] to the doctor's judgement.* (GP13, male, 45 years)
> *'Yes, but if you don't emphasise the importance or the statistics, then it's easy to stay in limbo […] So it's actually good that one strives as much as possible towards evidence-based ideas over […] what's the smart thing to do, or what is the wisest option to reach a good compromise.'* (GP15, male, 54 years)

> *'It's also dangerous, doing your own thing, because then it's just like the way it used to be… and you do wish that some things were sorted out.'* (GP 7, male, 56 years)

[1] DCGP: Dutch College of General Practitioners. In Dutch: 'Nederlands Huisartsen Genootschap (NHG)'.

GPs stated that it would be unrealistic that guidelines should specify for any possible disease combinations, but would feel better supported in the care for patients with multimorbidity when guidelines gave more details for diagnostic, treatment and management priorities.

Limitations from guideline adherence in patients with multimorbidity

Limited usefulness of guideline adherence in multimorbidity

There was agreement that guidelines were less useful for elderly patients and 'complex cases' of multimorbidity. GPs commented that guidelines were essentially not designed for these complex patients and felt that in these cases implementation was not as straightforward as in younger patients.

> *'The DCGP guidelines are […] not particularly applicable for the very aged, and also not for lots of things mixed up together.'* (GP24, male, 56 years)[2]

> *'The flipside of the coin is that these guidelines are not made for the 80 year olds.'* (GP 12, female, 58 years)

> *'As patients get on in years, I tend to adhere less faithfully to the strict norms in the DCGP guidelines for blood pressure and such things. And to say, now, let's just prescribe extra medicine on top of it all, I won't do that.'* (GP23, male, 51 years)[2]

A component of this limitation of guidelines was the issue of 'prevention'. GPs felt that adherence to guideline-recommended preventative measures was less appropriate in the case of older patients with multimorbidity and patients with a limited life-expectancy. This was more pronounced if these measures were accompanied by side-effects. They also questioned whether similar benefits could be expected from preventative measures as for younger or healthier patients. When GPs felt less convinced of the advantages of prevention, they would put less emphasis on this topic in the consultation. A sense of acceptance of limited therapeutic or preventative benefits was expressed if it concerned older patients.

> *'I think that I'd pay more attention to the preventative aspects with a younger patient, to see what's possible. Someone who's 55, who's had a heart attack and COPD and still smokes, I'd push harder for them to quit smoking than with the same person who's 75.'* (GP14, male, 63 years)

[2] DCGP: Dutch College of General Practitioners. In Dutch: 'Nederlands Huisartsen Genootschap (NHG)'.

'Many of those with multimorbidity take a substantial number of preventative medications [...] of which the benefit isn't clear, at least not immediately, and it's also the question whether you will experience that benefit, or whether you'll mainly get side-effects, or both.' (GP 1, female, 36 years)

'With a 40-something year old, the treatment aim is clear… to reduce risk over a long term period. But for an 80-something year old, it becomes less clear cut […] What can the patient get out of it, and also, what are the possible side-effects?' (GP6, female, 31 years)

'With the aged, a long-term treatment is...dubious. If it doesn't go well and smoothly, then there's totally no motivation for you to go through with it.' (GP 24, male, 56 years)

'In my opinion, blood pressure treatment causes a lot of side-effects. Like dizziness and falls. […] I think, better to have [systolic] pressure of 160 and not fall - that's more important.' (GP7, male, 56 years)

Guideline adherence conflicts with a patient-centred approach

Despite the need for guidelines, GPs often saw good reasons to ignore guideline recommendations in individual circumstances or to omit treatments in patients with multimorbidity. Consistent guideline adherence was perceived as an impediment to deliver individualised, patient-centred healthcare to patients with multimorbidity, which emerged as GPs' major objective in their care (described in detail in our previous paper[20]). This came forward in their inclusion of patients' preferences and circumstances in their management decisions, even when this meant to ignore guideline recommendations. Some GPs expressed this explicitly while many agreed with such comments.

'And that's the essence of what you're talking about. Not that this lady has osteoporosis and which pills according to the guidelines are the best - that's something I can look up myself, that's not so difficult. But the point is, this lady, who lives all alone, what is best for her, when does she have to relocate? What do we do in this situation? Should we arrange home nursing, or does she need to move anyway?' (GP 25, male, 56 years)

It was considered impossible to exhaustively grasp the complexity within guidelines that inevitably comes along with multimorbidity.

> *'The question is whether you can ever grasp the complexities of all the interactions between diseases in guidelines. […] And whether you can find something that applies to this specific patient in the guidelines, well, I fear the worst.'* (GP13, male, 45 years)

A perceived risk of working too much 'guideline-driven' is that items addressed in the guidelines will be automatically prioritised over patients' other important health problems.

> *'We have a strong tendency to keep working on the cardiovascular issues. […] And then you see these people leave the clinic and you think, OK, actually we should have done something about the osteoarthritis.'* (GP13, male, 45 years)

Concerns about the applicability of guidelines for multimorbidity

Scepticism was articulated on the applicability of evidence-based guidelines to patients with multimorbidity. Concerns were expressed that patients included in research and their specific circumstances are not comparable to patients with multimorbidity. Guideline recommendations following research results are not simply generalisable to patients with multimorbidity.

> *'For example, such a guideline for diabetes or hypertension is based on, I don't know, research on 40-60 year olds… with mono-morbidity, probably. I don't know if this is like this in all cases. But in general, that's what happens. And what's that worth for an 80 year old patient with multimorbidity? Nothing, in my opinion.'* (GP7, male, 56 years)

> *'There is of course completely no evidence for these patients, because no one knows if they are going to treat [high] cholesterol in someone who's 80 with asthma and who's had chemotherapy, for example. There's also nowhere where you can look that up.'* (GP7, male, 56 years)

Also, GPs commented that combining therapeutic regimens, originating from evidence-based guidelines written for single diseases, does not lead to an evidence-based combination for patients with multimorbidity. Guidelines can be conflicting, and often it is unclear how they relate to one another, which impedes using several guidelines for one particular patient.

'I think, OK, I can go all-out on treating each and every disease, but whether the sum of the parts actually results in a better level of care from my side, that's the question. So, that makes me a little more conservative, because I think, well - I'm not too sure about that.' (GP13, male, 45 years)

'All the indicators are for singular problems. That's how those are often studied, right? But in combination, much less. […] And what you should focus on - that's not really covered either.' (GP14, male, 63 years)

Empirical solutions

The disadvantages GPs perceived from guideline application to patients with multimorbidity resulted in several practical solutions, enabling them to provide continuous healthcare to these patients. This paragraph summarises the empirical solutions mentioned.

From their experience, GPs expressed a need to rely on their 'common sense' - a source of 'knowledge' that may complement the limitations of guideline application in multimorbidity. This implied making patient-centred decisions, accounting for the personal circumstances of patients with multimorbidity. However, relying on one's 'common sense' only was not considered acceptable anymore in the current era. Guideline adherence and applying 'common sense' needed to be in balance.

'[Multimorbidity] gives you a lot of freedom to use your experience and own ideas as a doctor to help the patient's problem. Otherwise you'd be much more tied to the evidence […] you get to a certain point when that's not as challenging to do.' (GP7, male, 56 years)

'With all of the guidelines available, you can use your common sense to say, well, I'd choose this one for this and that reason, that's easy to justify, or at least I think so. And then the guidelines are definitely not always followed, because common sense in the case of this patient… ' (GP11, male, 57 years)

'No, but that's not the reason that the guidelines shouldn't exist.' (GP15, male, 54 years)

'No, and the question is also, whether everyone's common sense is the same?' [All laugh] 'Probably not, so we all probably make different choices. […] That's how the guidelines arose. All the doctors, with their own common sense, thought that they were doing it right.' (GP 14, male, 63 years)

One GP described that an authorised guideline is not the only source providing support to GPs in the difficult decisions they need to make in patients with multimorbidity.

He suggested that regular refresher courses on complex topics could provide more knowledge and insight leading to guidance in a different way.

> *'A few extra courses on this subject would be of help to GPs, I think. And to support our common sense. […] So I think that [more] knowledge, […] without immediately having to set up a guideline for it, but just using [that knowledge] I think can also help.'* (GP14, male, 63 years)

Additionally, improvements could be made in guideline reporting, to increase their value for patients with multimorbidity. A GP proposed to have a ranking of importance made in recommended (preventative) measures for patients with multimorbidity, considering the seriousness of adverse results if they are not adhered to. The same GP proposed, with agreement of the other GPs in his group, that guidelines should more explicitly comment on their external validity. This could provide support to GPs *not* to adhere to guidelines for specified reasons or in specific situations – creating valid reasons to make patient-centred decisions, by applying their 'common sense'.

> *'You'd also want to know which interventions are actually the most critical, right? For example, administering an anti-coagulant with atrial fibrillation, that's what you almost always should do, in any case that's what I think, but I think you should also still do that with someone who's 88, because a stroke is a drama of course. And I think cholesterol for example is a different story, as is hypertension.'* (GP7, male, 56 years)

> *'Do you have the feeling that the guidelines help you to treat people with multimorbidity?'* (Moderator)
> *'No. It would be great if the guidelines would mention for whom it doesn't apply, and then I think you'd be shocked at the number of your patients that fall into this category.'* (GP7, male, 56 years)

Another GP tried to explain to his patients the evidence underlying guideline recommendations. In a conversation on how to translate guidelines into personal treatment choices, he let these well-informed patients' opinions influence decisions on whether or not to start new treatments – again coming to a patient-centred solution.

> *'If you look at the numbers needed to treat, for many of these things, these are around 20, 30, would be considered great, right? But when you discuss with those people, many end up declining the treatment […] many people have their own [well-informed] opinion.'* (GP13, male, 45 years)

Finally, permission to exclude patients with multimorbidity from regular pay-for-performance systems could reduce the burden of imposed, but inappropriate guideline adherence, and improve the quality of care delivered to patients with multimorbidity. In those focus groups where the issue of pay-for-performance was discussed, GPs agreed that guideline-derived incentives for patients with multimorbidity were undesirable and inappropriate.

> *'The legislation and the incentives are just completely irrelevant and not to the point if you're talking about quality.'* (GP15, male, 54 years)

> *'It would be good if these people with multimorbidity, and especially with complex diseases combined, were to be excluded from the tables. […] So you'd need another set of criteria, separate from the criteria for [relatively] healthy people with only one disease.'* (GP13, male, 45 years)

> *'What doesn't help are the performance indicators for diabetes care where you are forced, at the end of the year, to submit all the statistics for diabetes care, and are judged on […] how well the HbA1c has been controlled. Because that doesn't show that we take the patient [as a whole] and the prognosis into consideration.'* (GP 16, female, 44 years)

DISCUSSION

Summary

In this paper, we explored and described how GPs value evidence-based guideline application in patients with multimorbidity, i.e. patients for whom they had several potential guidelines to follow at the same time. GPs treasure the availability of guidelines in general, but at the same time expressed that guidelines do not cover the requirements needed to deliver complex care to patients with multimorbidity. They do not give sufficient opportunities to provide the desired individualised approach in multimorbidity, which may be considered as more important than adherence to the guidelines. Recommendations from single disease guidelines are not simply generalisable to patients with multimorbidity. When GPs apply guidelines for patients with multimorbidity, they incorporate patients' specific circumstances. Guideline-supported care to patients with multimorbidity can therefore be regarded as a good illustration of the use of the core values of primary care. This paper provides a new insight that, from their practical experience with patients with multimorbidity, GPs apply empirical solutions, such as balancing guideline recommendations with their 'common sense' and a patient-centred approach, to counteract guidelines' pitfalls.

Strengths and limitations

This study was performed by applying robust qualitative methods. Focus groups were guided by an experienced moderator with familiarity to the subject discussed. Participating GPs had been invited using a purposive sampling strategy. It is possible that GPs with a special interest in complex care, such as care for patients with multimorbidity, were more inclined to attend a focus group session than GPs without such an interest. This might have increased the vivacity of discussions, but participants were not selected on this criterion. Data collection proceeded until saturation was reached. The entire analysis was performed by two researchers, using the constant comparative analysis technique, which is an appropriate technique in qualitative research if new theory is to be generated.

Focus group discussions were held in Dutch and in the context of Dutch healthcare, thus providing views of participating Dutch GPs. The results do not allow generalisations to the primary care context in general. However, the resemblance of our GP sample to the Dutch professional GP group[24] does increase transferability of our findings.[25] GPs in countries with a healthcare system comparable to that in the Netherlands may experience similar problems from guideline application to patients with multimorbidity, and their practical answers to such puzzles might show similarities to the empirical solutions described in the current study. Future research should elaborate this. Some time span existed between data collection and writing of this paper, because it had not been planned originally to produce a separate paper specifically focusing on the role of guidelines applied to patients with multimorbidity. In the mean time, the number of new publications on this theme was limited. It seems unlikely that this 'publication delay' importantly influenced our findings. The role attributed to comorbidity in new (Dutch) primary care guidelines was not obviously different than before our data collection.

Our research question produced new insight into a research field without much preceding literature. This originality provides the major strength of our work.

Fitting the iterative nature of qualitative research, the idea to analyse the data regarding the current research question arose gradually. Although this theme was an explicit subject of discussions, participants were not made aware of it as additional research question beforehand. Would this have been the case, participants might have been overthinking the specific issue of guideline application to patients with multimorbidity consciously, which could have resulted in the expression of beliefs that remained unrevealed now. We find it unlikely that with such a scenario participants would have expressed clearly deviant ideas from the ideas they expressed here. However, it is not possible to establish if and to what extent our results would have been expanded or altered were this research question announced explicitly.

On most subjects discussed we found no obvious difference between beliefs expressed by GPs with different characteristics, with two exceptions. Discussions on the applicability

of guidelines for multimorbidity, and about the empirical solutions applied to overcome guidelines' disadvantages were mainly brought up by GPs with an academic affiliation. GPs without academic involvement did not express opposing views but accepted these beliefs and agreed with them in general. As a consequence, we conclude that there were no contrasting beliefs between 'academic' and 'non-academic' GPs, but that academic GPs were better able to articulate the tensions between patient-centred and guideline-directed care. This might be caused by a greater familiarity of researchers with the way guidelines are realised, and GP trainers' custom to reflect on their own practice as they do in the GP residency programme, which makes them 'trained' in expressing their beliefs. This may have helped in gaining valuable insights from these participants.
It came as some surprise that the collaboration with specialists did not feature strongly in the discussions. This may be due to the structure of the current study, focused on the role of guidelines, and the fact that GPs in the Netherlands identify strongly with the DCGP guidelines as 'their own'.[19] Our previous study, describing GPs' considerations and main aims in multimorbidity management, did include GPs' views on cooperation with specialists.[20]

Comparison with existing literature

The findings of this study help to reflect on the adequacy of 'guideline-based' modern medicine from the GP's perspective. Evidence-based guidelines are perceived as useful in general but several shortcomings are experienced in patients with multimorbidity. Important problems arise from discrepancies between recommendations based on single-disease guidelines, and that what is perceived by GPs as serving a particular patient with multimorbidity best. From a patient-centred work style GPs try to achieve shared decision making, they individualise treatments, and they may deliberately omit specific treatments. In the setting of a continuous clinical relationship, knowing the context of the patient informs intuitive judgements.[26] This 'knowing of the particular' is at the heart of general practice - but may be seen as contrasting with the principles of biomedical science, where it is explained what patients have in common, and ignores in what they differ.[27] However, the practice of evidence-based medicine requires integrating individual clinical experience with the best available external clinical evidence: good doctors need to rely on both.[28, 29, 30] This integration is exactly what was expressed by our participating GPs as an empirical solution to deal with the discrepancy between guideline adherence and providing optimal care to patients with multimorbidity.
To the best of our knowledge, no previous papers specifically analysed the value of guidelines for patients with multimorbidity as it is perceived by practitioners who use them in clinical practice. A few previous papers describing how GPs deal with multimorbidity reported briefly on the value of medical guidelines in this respect. Qualitative data have

been synthesised by Sinnott and colleagues, concluding that mixed feelings exist on the clinical utility of guidelines.[18]

Some previous studies demonstrated guidelines' limited suitability to patients with multimorbidity: they showed that the frequency and consistency of recommendations accounting for patients' comorbidity are low, and that they provide limited guidance in making treatment priorities.[10-12] These constraints, which were identified in literature reviews and on merely theoretic grounds, have now been exemplified by our qualitative data.

Two original studies, focusing on GPs' perspectives on care for older patients with multimorbidity, produced results that show similarities to our findings. Fried *et al.* described variable beliefs regarding benefits and harms of guideline-directed care among their participants. Those who expressed concerns did so regarding limited external validity, and the adverse events that may be caused by applying multiple guidelines. Additionally, guidelines' target outcomes may not be most relevant for patients with multimorbidity.[31] In a Dutch focus group study exploring 'GPs' feelings on deprescribing medication', participants also distinguished medication prescribed for symptomatic conditions and preventative medication. They experienced a lack of information regarding risks and benefits of preventative medication for patients with multimorbidity, and felt compelled to prescribe by the present guideline.[32]

The difficulties experienced in practice by our participating GPs led to suggestions how to make evidence-based guidelines better viable for patients with multimorbidity – a necessary step, since guidelines are indispensable in the current era, as was confirmed by the participants. Other papers describing barriers made some similar suggestions, for example accounting for the patient's context,[10, 30, 31, 33] focusing on generic instead of disease-specific outcomes,[34, 35] providing guidance in prioritising guideline recommendations,[16, 17, 32] and improving the external validity of clinical trials and guideline recommendations.[16, 36] In addition, it has been recommended to include more elderly people and patients with comorbidity in future studies,[16, 17] and to apply more cross-referencing between existing guidelines, in order to enhance guidelines' usefulness for patients with multimorbidity.[17] An innovative possibility is to apply the concept of 'pay-off time', predicting if a patient with limited life expectancy is likely to benefit from adherence to a particular guideline, by calculating the minimum time until its cumulative benefits exceed its cumulative harms.[37] These suggestions all address very well the guidelines' limitations mentioned by our participants.

'Complexity theory' has been used to implement interventions in the primary care setting, and yielded sustained effects in individualising the structure and processes of care towards individual values.[38, 39] This reflects the challenges GPs reported in our study to address the needs of patients. As their approach worked in different participating

practices, this would make 'complexity theory' a valuable approach to incorporate in the organisation culture of care of patients with multiple health problems.
Reformulating 'quality of care' for patients with multimorbidity and adapting pay-for-performance systems accordingly is a merely practical need to better address multimorbidity. It challenges current systems in which payment is based on adherence to guideline-based recommendations. This suggestion, raised by participants in our study, finds support in the literature.[31, 40] A new proposal from the current study is to make more use of post academic trainings focused on multimorbidity. This reduces the need to rely on guidelines only as a resource providing guidance in difficult treatment decisions.

Implications for research and/or practice

To conclude, inconsiderate adherence to guidelines is undesirable in the care for patients with multimorbidity, and would come at the risk of losing 'the art of medicine'. Nevertheless, evidence-based guidelines are indispensable components of modern medicine. Several suggestions have now been summarised how to improve guidelines' applicability to patients with multimorbidity, for example increasing and better reporting of the external validity in future research, and prioritising guideline recommendations. Patient-centred care provision demands adjusting professional tasks to a specific patient's needs. This requires practitioners' autonomy to deviate from guideline recommendations when appropriate, without negative financial consequences, especially in the case of multimorbidity. Facilitating such flexibility could help to accomplish the provision of patient-centred care to patients with multimorbidity, a much needed and desired pursuit by patients as well as GPs.

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Chapter 7

General discussion

GENERAL DISCUSSION

With a mixed methods approach, this thesis generated more knowledge on the epidemiology of comorbidity, its associations with disease-specific outcomes, and on general practitioners' (GPs') experience with multimorbidity in daily practice. The focus of this thesis was on the GP's perspective on multimorbidity, since this perspective had been relatively underexposed in the literature. The thesis had several aims:

- To describe the prevalence and incidence density of comorbidity in type 2 diabetes patients.
- To explore the long-term associations between comorbidity and longitudinal diabetes control parameters in type 2 diabetes.
- To study the considerations and main aims of GPs in their care for patients with multimorbidity, and to explore factors influencing their management of multimorbidity.
- To explore how GPs value guidelines when applied to patients with multimorbidity, and which benefits and barriers they experience from adherence to guidelines in these patients.

The first part of this thesis (**Chapters 2, 3, and 4**) studied multimorbidity quantitatively. It used type 2 diabetes mellitus as a 'case study' to describe its epidemiology, and to describe associations between several disease combinations and disease-specific outcomes. The qualitative second part of this thesis (**Chapters 5 and 6**) described GPs' experiences with and solutions for the management of multimorbidity in daily practice. For the interpretation of the overall study findings of this thesis, here the findings of the 'diabetes case study' from the quantitative first part of this thesis will be related to the findings of the qualitative studies from the second part and generalised to GPs' clinical decision making.

First, an overview is presented of the results of the research questions, with a discussion of the interpretation of the overall findings. The relevance of the findings in relation to the literature, and some strengths and limitations are discussed. Furthermore, the implications of the findings, both for future research and for daily practice in GPs' management of multimorbidity are described.

OVERVIEW OF THE RESULTS

Chapter 2 reported the prevalence and incidence density of a broad range of chronic comorbid diseases in representative, newly diagnosed type 2 diabetes patients in primary care. Both concordant (related - that is, cardiovascular) and discordant (unrelated) comorbidity were shown to be very common. It demonstrated that the diabetes patient population is heterogeneous in terms of comorbidity, and that the diabetes patient without (discordant) comorbidity is relatively rare. Chapter 3 explored the associations between longitudinal diabetes control parameters and the number and specific types of comorbidity in a primary care cohort of patients with type 2 diabetes. The simple sum of comorbid diseases did not show an unfavourable association with trends of HbA1c or systolic blood pressure over five years, but specific types of comorbidity (i.e., musculoskeletal disease, cardiovascular disease) did. Chapter 4 showed that diabetes patients with comorbid COPD have different trends of systolic blood pressure over five years compared to diabetes patients without COPD, an effect that was modified by socioeconomic status and body mass index.

Chapter 5 described that applying a patient-centred approach is the main aim of GPs in their care for patients with multimorbidity, which helps to oppose some potential pitfalls of multimorbidity. Patient-centredness was achieved by individualising decisions and placing medical considerations in a broader perspective. Fragmentation of care was identified as an important risk in multimorbidity, and the combined presence of somatic and mental health conditions was perceived as a particularly difficult combination. The existence of a personal relationship between doctor and patient was supportive for the management of multimorbidity. In Chapter 6 it was explored how GPs value guidelines when these are utilised for patients with more than one disease. Guidance from guidelines was appreciated in general, but guidelines were perceived as insufficient to guide the complex care needed for patients with multimorbidity. GPs doubted the applicability of guidelines for patients with multimorbidity and often considered preventative measures as inappropriate. They integrate clinical experience with the best available evidence in patients with multimorbidity.

INTERPRETATION OF THE OVERALL FINDINGS IN THIS THESIS

Most of the work in this thesis was explorative research without much similar literature preceding it. In this thesis, mixed methods were applied. Especially in a research area with many blanks, as is the case in multimorbidity,[1] both information on the frequency of the issue under study and information on how and why things occur under daily practice circumstances is needed. A mixed methods approach helps in gaining a deeper understanding on both types of missing information, and precisely the combination of

quantitative and qualitative results can produce a broader insight into the complex issue of multimorbidity. In the observational research in the **first, quantitative part of this thesis**, type 2 diabetes was chosen as a case study to examine the epidemiology of comorbidity, and the associations of comorbidity with the outcomes of an index disease among patients receiving regular healthcare. Type 2 diabetes is a common chronic disease, generally taken care of in primary care. It has quantifiable outcome measures enabling comparison between patients with and without (specific types of) comorbidity. Such outcome comparisons were made in Chapters 3 and 4. A causal relation of the findings reported in this thesis' first part cannot be inferred from observational research. Neither does the explorative nature of the studies in this part justify the suggestion of concrete recommendations to change daily practice instantly. However, it has become clear that diabetes patients who also have (discordant[2]) comorbidity are the rule rather than the exception. Moreover, the findings emphasise that the presence of comorbidity can interact with diabetes outcomes. Nevertheless, evidence-based medical guidelines derive their recommendations from randomised controlled trials (RCTs), but patients with (discordant) comorbidity are generally excluded from these RCTs.[3, 4] Within the framework of this thesis, it was not possible to analyse additional index diseases and make analogous examinations of associations between their comorbidity and disease-specific outcomes. But it is to be expected that, with a different index-disease, interactions between some types of comorbidity and other disease-specific outcomes will also exist. This could be an area for further study. Distinct associations found in early explorative work may define the focus for deeper investigations in future research, and the methods applied and findings reported in the current thesis may be considered as a starting point in this respect. Notwithstanding, current guidelines do not yet specify how comorbidity may influence management of diabetes or other chronic diseases.[5-7] As has been suggested for diabetes[7, 8] and for COPD,[9] guidelines for other diseases should also regard a patients' comorbidity as a patient characteristic that should be accounted for in personalised disease management.[10]

Hence, it is obvious that comorbidity has interference with the management of other chronic diseases, but evidence-based recommendations how best to address this issue in daily practice, yielding optimal health outcomes, are not yet available. Current clinical guidelines hardly provide guidance in how to prioritise recommendations when patients have multiple diseases.[11, 12] Therefore, the **second part of this thesis**, containing the results of qualitative research, sought to employ GPs' empirical knowledge on the daily practice management of multimorbidity. Patients desire patient-centred care that explores their needs, pursues an integrated understanding of them, and promotes health, in a mutual agreement and a continuous relationship with the doctor.[13, 14] Patients with multimorbidity desire continuous, individualised, communicative care, and

need help in prioritising competing demands,[15] while they experience problems with fragmented care.[16-24] Studies of the perspective of healthcare professionals who deal with multimorbidity on a daily basis have been relatively absent in the literature. The viewpoints of GPs, accessible gatekeepers with an overview on a patient's entire health status, were expected to produce valuable new insights into the care for patients with multimorbidity. Such a professional frame of reference was necessary to gain understanding in how generalists apply their broad knowledge and skills to guide patients with multimorbidity in the healthcare system.

After articulating GPs' goals in the management of patients with multimorbidity (**Chapter 5**) and GPs' views on the value of guidelines in this respect (**Chapter 6**), the qualitative part of this thesis provided insight in how to address dilemmas and complexities resulting from multimorbidity based on this empiricism. In this way it complements some gaps in evidence-based multimorbidity management. By prioritising patient-centredness and using their 'common sense', GPs avoid fragmentation of care and insensible implementation of disease-specific recommendations from guidelines that are not directed at patients with multimorbidity, and not expected to provide them more benefits than harm. GPs perceived strict ('uncritical') guideline adherence as a barrier to provide patient-centred care to patients with multimorbidity. In the management of multimorbidity in daily clinical practice, they rely on their knowledge of the particular patient and their continuous relationship with him or her, and aim to achieve shared decision making. This empirical, patient-centred strategy helps them to overcome several barriers that the GPs in this study linked to multimorbidity. The existing shortcomings in evidence-based guidance on how to provide best care to patients with multimorbidity (described in **Chapter 1** and above) are thus overcome by making clinical judgement, informed by knowledge of the patient, and GPs' practical experience. This is what has happened in primary care throughout the decades and what should be retained in future care for patients with multimorbidity. It can be seen as practising evidence-based medicine at its best: it necessitates the integration of best available clinical evidence with individual clinical experience.[25-27] From the GP's perspective, this is how knowledge on multimorbidity meets daily practice.

RELEVANCE OF THE FINDINGS IN RELATION WITH THE LITERATURE

The recording of outcome data of type 2 diabetes in primary care has been performed over a long period of time in the Nijmegen Monitoring Project (NMP) practices in the Nijmegen region. These practices have shown to provide good quality diabetes care.[28] Combining this with the longitudinal morbidity recording in the Nijmegen Continuous Morbidity Registration (CMR), existing since 1967, resulted in a unique research facility to study

associations between diabetes control parameters and a wide range of chronic comorbid diseases.[29, 30] A dynamic cohort was realised, in which the presence of comorbidity in diabetes patients could be studied over time, that is, pre-existing comorbidity could be distinguished from incident comorbidity, and these different types of comorbidity could be linked to longitudinal diabetes control parameters with an extensive follow-up period. No previous studies were identified that provide a thorough description of comorbidity and its development over time in patients with diabetes. Incidence data of (discordant) comorbidity in diabetes had not been reported at all. Pre-existing (i.e., prevalent) and incident comorbidity may interfere with the management of diabetes - or another index disease - in different ways, which makes it important to distinguish between the two types of comorbidity. Medical records in general practice have an overview of the full range of morbidity, which makes the primary care setting ideally suited to study comorbidity of an index disease extensively.

The cohort comprised an unselected group of adult patients in primary care with a recent diagnosis of type 2 diabetes, and no exclusion based on age. In addition, any type of chronic comorbidity was included. These methodological choices made this cohort representative for the type 2 diabetes population at large. Including only newly diagnosed diabetes patients facilitated the incidence reporting of comorbidity before and after the diabetes diagnosis. Moreover, it resulted in a prevalence estimation of comorbidity which was different from a design that would have included patients with diabetes since many years. The prevalence of comorbidity in diabetes patients reported in Chapter 2 of this thesis was equal to[31] or higher than[32, 33] prevalence rates reported previously. The high prevalence and incidence density of comorbidity found in this study are notable, precisely since this cohort was not a selected population in secondary care, where a higher burden of comorbidity may be expected. The most important explanation is that in the studies in this thesis, any type of chronic disease was included as comorbidity, in contrast with other studies.[33, 34] Some papers published after the work in Chapter 2 reported similar rates of comorbidity in type 2 diabetes patients.[35-37]

Including only a (random) selection of comorbidity gives an underestimation of the total amount of comorbidity. In the studies reported in this thesis, chronic diseases that are not very prevalent on itself were also included as comorbidity. This allowed, for example, the summing up of diseases that, all in a different way, may affect patients' possibilities for self-management of diabetes - resulting altogether in a prevalence of 4%, a substantial proportion of the diabetes population. Chapter 2 furthermore reported that discordant conditions altogether outnumbered concordant conditions in diabetes patients, a finding that was confirmed in later publications that also considered a broad range of comorbid conditions.[35-38] These findings emphasise that presuming the existence of the 'typical' diabetes patient is unjustified.

Chapters 3 and 4 elaborated on these observations, by showing different patterns of diabetes control parameters according to diabetes patients' comorbidity profiles. They demonstrated for example differences in these parameters over time for diabetes patients with different numbers of comorbid diseases, and for diabetes patients with or without cardiovascular disease, musculoskeletal disease, and COPD. Some of these associations were modified by patients' socioeconomic status and/or body mass index. Among the few papers that also examined associations between comorbid diseases and diabetes control parameters, analysis of patients characteristics such as SES was generally absent.[39, 40] This stresses that a lot of research remains to be performed on the personalisation of the management of chronic diseases.

In Chapters 5 and 6 it was described that patient-centredness is GPs' priority in their care for patients with multimorbidity. They allow their 'common sense' to interfere when it is questionable if adhering to evidence-based recommendations would increase patients' health status. The approach pursued by GPs fits well to what patients with multimorbidity themselves prioritise in their healthcare.[15, 16] Later qualitative studies focusing on the GPs' perspective of the management of multimorbidity in daily practice also emphasised the importance of patient-centredness.[41] Similar to the findings in the qualitative part of this thesis, a balance between adherence to prescription recommendations from guidelines and providing patient-centred care to patients with multimorbidity was expressed in a recent qualitative paper studying GPs' decisions related to prescribing medication for this patient group.[42]

Patient-centredness in primary care has been defined as containing several dimensions, namely regarding the patient as a whole person from the biopsychosocial perspective, looking for a common ground between doctor and patient, and building a therapeutic alliance (continuous doctor-patient relationship).[43] Shared decision making is a component of patient-centred care. It implies partnership between doctor and patient, the provision of medical and personal information, communication (including negotiation), and agreement.[44-46] Another component of patient-centredness is continuity of care. Patients with multimorbidity have high consultation rates.[47] In 1980 already, McWhinney described that clinical decision making requires both individualisation and generalisation. He defined several factors in the clinical decision making process that are typical for primary care, including the use of knowledge of the patient and his context, and a continuous relationship with the patient.[48] Two decades later, Starfield and colleagues showed that healthcare utilisation is larger for a patient's comorbidity than for a specific index condition, and that comorbidity has a greater burden on primary care than on specialist care. They consequently stressed the importance of a continuous primary care context for patients with multimorbidity, and of focussing on patients' overall healthcare

needs, not just on all separate disease needs.[49] A recent study showed that greater continuity of care for patients with multimorbidity can be promising in the current era with its increasing burden on financial resources, since it was associated with lower hospital utilisation.[50]

The principles of patient-centredness - listening to patients, informing and respecting them, involving patients in their care, and valuing their wishes without mindlessly enacting them - are not in contradiction with evidence-based medicine, which requires both generalisations and the art of knowing the particular of individual patients.[25, 26, 51] In the care for patients with multimorbidity, both components are indispensable.[52]

STRENGTHS AND LIMITATIONS OF THE THESIS

Some important strengths of the work presented in this mixed methods thesis have been discussed in detail earlier in this chapter. A major strength is the robustness of the methods applied, both in the quantitative and in the qualitative parts of this thesis. In the quantitative part, this consisted of the utilisation of data originating from a reliable primary care research network, resulting in representative, longitudinal data, and a long follow-up period. Diabetes control parameters were combined with comorbidity data, and clear definitions were used. In the qualitative part, an iterative process of participant sampling, data collection and analysis was applied, as required in qualitative research. The composition of the purposive sample of participating GPs increased the transferability of the findings. Data collection proceeded until saturation was reached.

Several limitations of the work described in this thesis need to be acknowledged too. Due to changes in diagnosis and treatment of diabetes over time, patients in the early phase of the dynamic cohort of diabetes patients (in the quantitative part of the thesis) may not be fully comparable to those later in the cohort. This type of limitation however is inherent to any type of observational research with a long follow-up period. Sensitivity analyses correcting for the time period did not result in significant changes of the major outcomes.

The longitudinal outcomes in the diabetes case-study in the first part of this thesis are influenced by prescribed medication and non-pharmacological interventions for the treatment of diabetes and comorbid diseases. It was not possible to compare medication and lifestyle interventions between diabetes patients with and without specific types of comorbidity in this dynamic cohort study. As a result, if and how potential differences in therapeutic regimes may have contributed to the outcomes observed cannot be explained. However, this observational work aimed to explore associations occurring under daily practice circumstances (in the absence of an intervention), and comparison of therapeutic regimens between groups fell beyond its scope. Current guidelines recommend similar

targets for all diabetes patients, regardless of their comorbidity profile. GPs may however deliberately adapt the therapeutic goals based on patients' comorbidity.[41, 53] Therefore, should it be found in future studies that the presence of a specific number or type of comorbidity appears to be a reason for not prescribing the recommended diabetes treatment intensity (i.e. less strict glucose-lowering or antihypertensive treatment), then this would be an interesting finding to report on itself. When prescriptions occur more flexible by intention, as a result of existing comorbidity, medication prescriptions should preferably be analysed as outcome measures instead of handled as a covariate.

Inherent to qualitative studies is that it reveals the ideas, perceptions and intentions of participants in the study. It does not assess actual behaviour. Consequently, the results in the qualitative second part of this thesis describes GPs' ideas, not measurements of their actual behaviour. These are important to assess first when their content is not yet well known. Assessment of GPs' actual behaviour regarding multimorbidity management could be subject to further research. This could occur for example by analysis of clinical reasoning when GPs would be asked to articulate their lines of reasoning in providing care to patients with multimorbidity.

The most important strength of the research reported in this thesis is its innovative aspect. Both the quantitative and the qualitative part of this thesis did not have much comparable work preceding it. The research reported here generated more knowledge on the epidemiology of multimorbidity, and identified associations between specific combinations of diseases and longitudinal disease outcomes. It also applied GPs' empirical solutions how to deal with multimorbidity's complexities. By applying these mixed methods, this thesis provided suggestions for improvements in the care for patients with multimorbidity. Multimorbidity is nowadays often considered a research priority, after the prosperous days of evidence-based medicine with its focus on single diseases, and in the light of the ageing population. The thesis contributed to the research field and implications for future research are defined.

FUTURE PERSPECTIVES

Based on the studies presented in this thesis, some important points of action can be defined for further research in multimorbidity and for the improvement of care for patients with multimorbidity. The findings also have implications for future medical guidelines.

Implications for research

The explorative quantitative research in this thesis may be followed by further examination of distinct associations found. For example, the interaction between type 2 diabetes,

COPD, longitudinal diabetes control parameters, and patient characteristics such as socioeconomic status and body mass index could be studied in more detail in larger primary care cohorts of patients with both diseases present. COPD-specific and generic outcomes could be added as outcome measures. Associations between diabetes and musculoskeletal diseases, diabetes and cardiovascular diseases, and diabetes and the number of comorbid diseases could also be elaborated, focusing on their interaction with demographic patient characteristics. Other diseases than diabetes could be studied as index disease too. Now that the importance of comorbidity as a patient factor possibly influencing outcomes of other diseases is increasingly being recognised, but little representative data quantifying such associations are available, it is important that disease-specific outcomes are studied in relation to comorbidity. Such actions could help in the development of personalised disease management, with recommendations accounting for specific types of comorbidity and other patient characteristics.

Some observations regarding research in multimorbidity in general practice need to be made. Although the management of multimorbidity is inherent to primary care, and publications on this topic have been appearing since a long time, the impressive increase in the interest for this issue in the scientific literature in the last two decades demands clear definitions and careful reporting of methodology, in order to optimise comprehensibility. Improvements can and need to be made in this respect. The concepts of 'chronicity' and 'chronic disease' lack a generally accepted definition. Consistent application of a code list with chronic conditions that was designed for primary care could enhance uniformity, although this list lacks a desirable elaboration of 'personalisation' of a chronic disease.[54] Chapter 2 of this thesis provided an example of how personalisation of 'chronicity' was implemented, by making a distinction between invariable and conditional chronic conditions. Information in the electronic medical records in a practice-based research network can be employed to distinguish whether or not a specific patient experiences a chronic course of a 'conditionally' chronic disease, i.e. from which either episodic or chronic courses occur (for example, asthma and gout), or from which patients may recover (for example, depression).

Comparison between multimorbidity studies is hampered by inconsistent use of definitions of 'chronic disease' and 'multimorbidity', which influences prevalence data.[55-57] The absence of a PubMed MeSH term for 'multimorbidity' further complicates this and it should therefore be introduced to improve consistency and tracing of literature. In the mean time, researchers should adhere to definitions for 'comorbidity' (referring to the presence of an additional condition in a patient with an index disease) and 'multimorbidity' (the co-existence of several diseases at the same time) that are widespread and generally accepted in primary care multimorbidity research, such as proposed by Van den Akker *et al.*[57-59]

When studying the impact of comorbidity on an index disease, it is important not to include just a (random) selection of comorbid diseases, but rather a broad range of comorbidity, which reflects the entire comorbidity burden in patients with the index disease, resulting in better representativeness.

Researchers who consciously reflect on the issue of multimorbidity are more likely to adhere to such recommendations. However, a shift also needs to be made by researchers oriented on specific diseases, since many patients with any type of chronic disease will have multimorbidity. After the introduction of 'evidence based medicine' as a new paradigm, the focus on single diseases has brought the risk of 'siloing' of care for patients with multimorbidity.[12] A new direction in evidence based medicine is important so that it yields research results that are more relevant, useful and valid to patients with multimorbidity – which is not the case with the current focus on following single disease algorithmic rules, aimed at improving disease-specific outcomes.[26, 60, 61]

Research in multimorbidity is complex, due to the vast heterogeneity in the spectrum of disease combinations. This is further complicated by the possible influence of patient characteristics such as age, sex, socioeconomic status, etcetera, on various outcomes. There is a need for more generic research outcomes, such as physical functioning and quality of life, in order to increase its relevance for patients with multimorbidity.[12, 62]

Possibly the ideal setting for studying multimorbidity is primary care. Collection of routine daily practice data in primary care, in the absence of an intervention, may yield longitudinal data containing patients' full range of morbidity. Such data have a higher percentage of missing values than data collected in a randomised trial, although when collected in experienced registration networks this can be largely reduced. Under randomised controlled trial circumstances, data collected both in intervention and in control groups have a higher chance of being slightly influenced by altered behaviour of doctors and / or patients. In the primary care setting, it would be possible to use wide inclusion criteria. These possibilities offer the advantage of producing data with good representativeness, since routine care is provided, which would be reflected in the data. Strict exclusion criteria limit the external validity of the findings. Future intervention studies designed under such primary care circumstances would ensure better generalisability of the results for patients with multimorbidity: they give a better representation of the general population (with multimorbidity) than a secondary care population. In this way they could address a major pitfall of current trials and subsequent guideline recommendations.[60, 63]

To facilitate research comparing outcomes between patients with and without comorbidity in addition to an index disease, collection of disease-specific outcomes should ideally occur in addition to generic outcomes. This requires extensive recording of routine data in well-equipped practices. Primary care research networks are a perfect setting for the collection of this type of data. Ongoing investments in primary care research networks

are needed to allow the generation of such extensive datasets, and are important to improve the relevance of future research for patients with multimorbidity.

Supported by sophisticated ICT systems with powerful analytic possibilities, the realisation of 'big healthcare data' (large datasets with patients' routinely collected health status data) in research facilities is currently experiencing an exponential increase. These 'big datasets' offer opportunities for large-scale observational research, and may result in more knowledge on the epidemiology of multimorbidity, its effects on disease control parameters, and more evidence-based personalised therapeutic recommendations accounting for comorbidity and other patient characteristics. An important condition for these 'big data' to produce applicable evidence for patients with multimorbidity is that they will be sensibly organised for this purpose. Not only the capacity to collect data, but also the availability of appropriate methods to analyse them need to be well developed to result in an optimal benefit. The quantitative methods applied in this thesis, such as the clear definitions applied including a distinction between invariable and conditional chronicity; categorising diseases in clusters; and distinguishing between concordant and discordant comorbidity, may serve as a starting point for further developing such methods.

Implications for guidelines

Research results inform clinical guidelines. Given the results in this thesis, the relative ignorance of (discordant) comorbidity in evidence-based diabetes guidelines is inappropriate and should be improved. Guidelines should better explicate how comorbidity may interfere with the management of chronic diseases and adjust recommendations accordingly. The findings in this thesis can give an incentive to this shift, although further investigation of associations between comorbidity, disease specific outcomes, and other patient characteristics is needed to justify concrete recommendations. It may contribute to the development of personalised chronic disease management, by formulating different therapeutic approaches that are appropriate, or should be prioritised, for patients with a specific comorbidity burden.

If evidence justifying concrete comorbidity-specific recommendations in guidelines is not available, then this should be made explicit. It is important that guidelines start to better explain their external validity so that it is clear to what extent recommendations are covered. A disease-specific focus in evidence-based guidelines would in general be more promising when no or only concordant comorbidity exists, than when discordant comorbidity is present. Importance of personalisation of disease management for patients with discordant comorbidity (e.g., a patient with mental health problems and a malignancy plus a chronic respiratory disease) should receive more emphasis in guidelines. Current single disease guidelines provide numerous recommendations for patients with multimorbidity. Empirical suggestions from the second part of this thesis on how

to improve guidelines for patients with multimorbidity included the formulation of a ranking of importance in guideline recommendations when these add up if patients have multiple diseases. The abovementioned adjustments would help practitioners when assigning priorities in their care for patients with multimorbidity.

Implications for practice

The diabetes case study showed that type 2 diabetes and COPD, both common chronic diseases with substantial combined occurrence, interfere with one another. The same applied for diabetes patients with comorbid musculoskeletal disease, an interaction possibly originating from a reduced ability of these patients to do physical exercise. Diabetes patients with comorbid cardiovascular disease showed to have consistent unfavourable courses of longitudinal systolic blood pressure from the diabetes onset onwards compared to diabetes patients without cardiovascular disease. In these cases of concordant comorbidity, concordant treatment strategies (all addressing metabolic / cardiovascular control) may be more important and more promising than in cases of discordant comorbidity. For the discordant types of comorbidity (e.g., diabetes and COPD, and diabetes and musculoskeletal disease), disease management needs to be more personalised. Ongoing research is needed to elaborate on the practical consequences of the specific associations found in the studies in this thesis. It is likely that future studies, describing other index-diseases than diabetes, will similarly result in an extensive co-occurrence of chronic diseases, and will show interactions between disease-specific outcomes. What needs to be added to the knowledge on multimorbidity, is if and how generic patient outcomes, such as quality of life, are influenced by the presence of comorbidity. Evidence lags behind in defining which approach suits best to which multimorbidity profile – and since the possible disease combinations are endless this is likely to remain the case.

However, the observation in the quantitative part of this thesis that not just an increasing number of diseases negatively influenced long-term diabetes control parameters, but that specific types of comorbidity did, stresses that diabetes care provided by GPs is part of general healthcare. Patient-specific factors intervene in the care that is directed to 'whole persons'. With an increasing amount of morbidity, the complexity of providing healthcare to a particular patient increases. This was especially perceived by GPs when somatic and mental health conditions co-exist in a patient. The substantial presence of comorbidity in type 2 diabetes patients - as shown in this thesis - implies that managing one common chronic disease requires simultaneous management of comorbidity. Hence a 'one-size-fits-all' approach is insufficient. When multimorbidity exists, it is necessary to deviate from the single-disease focus, and to provide patient-centred care by following a specific patient's needs.

Knowing that the evidence-base of guideline recommendations for patients with multimorbidity is often limited, preventative measures were considered inappropriate by GPs in many cases, especially when concerning older patients with multimorbidity. Based on the findings described in this thesis, adopting a reserved attitude towards preventative measures that are suggested in single disease guidelines seems sensible when these are administered to primary care patients with multimorbidity - as long as the evidence for expected benefits from these measures is insufficient for patients with multimorbidity, and care is provided in a patient-centred way.

GPs' empirical solutions to respond to the evidence gap for multimorbidity are to integrate clinical experience and a good 'common sense' with the best available evidence. This strategy is what defines 'evidence-based medicine', and it deserves more attention in clinical training. Also clinical decision making deserves more attention in doctors' professional development.

Providing patient-centred care to patients with multimorbidity helped GPs to counteract some potential pitfalls of multimorbidity, such as fragmentation of care. It may seem an obvious goal in the management of complex problems. However, to bring this into practice, advanced skills in communication and shared decision making are needed. Broad (generalist) medical knowledge needs to be complemented with the ability to integrate knowledge on diverse topics. By increasing the attention for these necessary skills, the care for patients with multimorbidity could be improved. This requires intensive training during medical education, and doctors' personal dedication to provide continuous care. Post academic trainings for GPs on topics related to multimorbidity and complex care (for example, courses on polypharmacy or multidisciplinary case reviews) could be employed more frequently, and could supplement single disease guidelines, which have obvious shortcomings for multimorbidity.

In addition, for GPs to be able to provide sensible care to patients with multimorbidity, it demands from policymakers the flexibility and approval that GPs may deviate from single disease oriented management strategies in patients with multiple diseases, without negative financial consequences.

Modern technology such as telemedicine, introduced for various specific conditions, improves quick access to healthcare[64] and patients' health behaviour and health status.[65] For patients with multimorbidity, 'e-health' could be of added value if it would address specific needs arising from multimorbidity. Patients with multimorbidity would like to make use of such tools in an integrated way, so that it covers not just the needs of one specific disease among their total disease burden.[66] The technology should facilitate communication, enhance a shared decision making process, and improve coordination of care. Strategies have been developed to promote patient-centred aspects in primary care consultations with patients with multimorbidity.[67] In future interventions, the core

values of primary care should be retained to optimise multimorbidity management.[68, 69] This means commitment to the person instead of a focus on specific diseases, continuity of care and responsibility, and clinical freedom allowing practitioners the flexibility to make difficult choices between competing priorities.[70]

CONCLUSIONS

This thesis studied multimorbidity from the GP's perspective. It showed a high prevalence and incidence density of comorbidity in type 2 diabetes, implying that the 'typical' diabetes patient does not exist. Management of one chronic disease requires simultaneous management of comorbidity, both the concordant and the discordant types. Ongoing research is needed to further disentangle associations between specific types of comorbidity. Studies in this thesis described some distinct disease combinations affecting longitudinal diabetes control parameters under routine primary care circumstances.

From the viewpoint of Dutch GPs, disease-specific guidelines do not sufficiently address the complexities occurring when patients have multimorbidity. A patient-centred approach is pursued in the management of multimorbidity, but contrasting with close adherence to current guidelines. Complementing evidence-based guideline recommendations with clinical experience and with knowledge of the individual patient, in a patient-centred way, is necessary for the care for patients with multimorbidity in primary care.

Future research and guidelines should be improved so that they have better applicability for patients with multimorbidity. At the same time, necessary skills to bring the abovementioned recommendations into practice should be taught in medical training programmes.

To summarise the implications for multimorbidity from the GP's perspective: ongoing research is needed to gain better insight into patterns of comorbidity and their consequences for patients, both on disease-specific and on generic health outcomes. Yet practice is likely to remain ahead of science. Relevant and applicable evidence evolving for any multimorbidity profile is an unrealistic scenario. Precisely when there is multimorbidity, a patient-centred approach is important - focusing on the needs, preferences, and risks of a specific patient. Supported by a continuous relationship with, and knowledge of the patient, an accessible GP may be the designated professional to help the patient with multimorbidity navigate through the abundance of diagnostic and therapeutic options, and help to prioritise options in order to establish the best 'fit' to a particular patient's situation.

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Chapter 8

Summary

SUMMARY

This mixed methods thesis described multimorbidity in primary care with a focus on the general practitioner's (GP's) perspective. The aims were:

- To describe the prevalence and incidence density of comorbidity in type 2 diabetes patients.
- To explore the long-term associations between comorbidity and longitudinal diabetes control parameters in type 2 diabetes.
- To study the considerations and main aims of GPs in their care for patients with multimorbidity, and to explore factors influencing their management of multimorbidity.
- To explore how GPs value guidelines when applied to patients with multimorbidity, and which benefits and barriers they experience from adherence to guidelines in these patients.

In the **first part of this thesis**, associations between type 2 diabetes and chronic comorbid diseases were described as a case study. In the **second part of this thesis**, GPs' experiences with and solutions for multimorbidity in daily practice were explored.

Chapter 1 gave an introduction to the theme of multimorbidity. It sketched some problems arising from multimorbidity on the patient and the practice level. The description of the evolvement of knowledge on multimorbidity in the research field and the remaining gaps in knowledge led to the formulation of the research questions for this thesis.

Chapter 2 reported the prevalence and incidence density of a full range of chronic comorbid diseases in a representative cohort of type 2 diabetes patients in primary care. Both concordant (related - that is, cardiovascular) and discordant (unrelated) comorbidity were shown to be very common. Once diabetes is diagnosed, almost 85% of these patients had one or more other chronic diseases, and after excluding the concordant cardiovascular diseases this was still over 70% of patients. A high comorbidity burden (defined as three or more additional diseases on top of the diabetes) was present in approximately a half or a quarter of the diabetes patients when any type of comorbidity, or discordant comorbidity only was counted, respectively. In the first year after the diabetes diagnosis, a first comorbid disease was diagnosed in a quarter of the patients who had no comorbidity during the diabetes diagnosis. Only chronic diseases were counted as comorbidity. For those diseases that may but do not need to follow a chronic course, such as gout or migraine, chronicity was identified on the patient level based on information from patients' electronic medical record. Diseases were categorised in disease clusters,

based on the ICPC-classification with separate clusters for malignancies and infectious diseases. Prevalence and incidence density of comorbidity was also calculated for disease clusters. Highest prevalence rates at the time of the diabetes diagnosis were reported for cardiovascular diseases (64%) and musculoskeletal diseases (31%). This study showed that the diabetes patient population is heterogeneous in terms of comorbidity, and that the diabetes patient without (discordant) comorbidity is relatively rare. Consequently, the relative ignorance of (discordant) comorbidity in evidence-based diabetes guidelines is inappropriate. Guidelines should better explicit how comorbidity may interfere with diabetes management, which may be the case for discordant comorbidity especially, and should adjust recommendations accordingly.

In the same primary care cohort of patients with type 2 diabetes, **Chapter 3** explored the associations between longitudinal diabetes control parameters and the number and specific types of chronic comorbidity. A mixed model analysis technique was applied to compare longitudinal trends of HbA1c and systolic blood pressure (SBP) during five years of follow-up between groups of diabetes patients with different comorbidity profiles. The simple sum of comorbid diseases did not show an unfavourable association with diabetes control parameter trends over five years, but specific types of comorbidity did. Diabetes patients with comorbid musculoskeletal disease had statistically significantly higher HbA1c values after five years, with lower values around the diabetes diagnosis, compared to patients without comorbid musculoskeletal disease. Diabetes patients with comorbid cardiovascular disease had significantly sustained elevated values of SBP from the diabetes diagnosis onwards, compared to diabetes patients without comorbid cardiovascular disease. The number of comorbid diseases was significantly associated with the five year trend of SBP (not that of HbA1c), with highest values after five years for diabetes patients without comorbidity, and effect modification by socioeconomic status. Causal relations cannot be inferred from the explorative, observational design of this study. It was hypothesised that the reduced ability for physical exercising could explain the increasing HbA1c values over five years among the patients with comorbid musculoskeletal disease, and that the concordance of the cardiovascular comorbidity explained the results among this comorbidity group on the longitudinal SBP outcomes. The observation that not just the sum of diseases negatively influenced the course of diabetes control parameters, but that this did occur under presence of specific types of comorbidity, emphasised that the diabetes care provided by GPs is part of general healthcare delivered to 'whole persons', i.e. 'person-centred care'. Apparently, the patient-specific context intervened. GPs integrated disease-specific and generic patient characteristics and treatment goals as part of diabetes-specific care. After further investigation of the patterns observed, these findings may

contribute to the development of personalised diabetes management by formulating different therapeutic approaches that are appropriate for diabetes patients with a specific comorbidity burden.

In **Chapter 4**, associations between comorbid COPD and longitudinal diabetes control parameters over five years of follow-up were explored in the type 2 diabetes patients cohort. Trends in HbA1c and SBP were compared with mixed model analyses between patients with and without comorbid COPD. Subgroup effect analyses explored potential effect modification of these trends (according to presence or absence of COPD) by age, sex, body mass index, and socioeconomic status. It showed that diabetes patients with comorbid COPD have different trends of SBP over five years compared to diabetes patients without COPD, an effect that was modified by socioeconomic status and body mass index. In contrast to diabetes patients without COPD, in whom an increasing body mass index is associated with increasing SBP levels, the trend of SBP in diabetes patients with comorbid COPD is defined more by the socioeconomic status than by the body mass index. Type 2 diabetes and COPD, both common chronic diseases with substantial combined occurrence, interfere with one another. Ongoing research is needed to further disentangle the complex associations between comorbidity of diabetes, COPD, diabetes control parameters, and the other patient characteristics; and to define how this translates into practical recommendations. It is clear however that the interference of these two common chronic diseases deserves attention from healthcare professionals taking care of patients with either disease, and that comorbidity needs to be recognised as a patient characteristic with possible influence on disease-specific outcomes of an index-disease.

The **second part of this thesis** contained qualitative research. A focus group study was performed with a purposive sample of Dutch GPs to ensure heterogeneity in characteristics such as age, sex, and urbanisation among the participants. Exploration of their considerations and main objectives in the management of multimorbidity, and factors influencing this management was the first aim. Second aim was to explore how GPs value guidelines when applied to patients with multimorbidity, and which benefits and barriers they experience from adherence to guidelines in these patients. In the iterative qualitative process, in which data collection and analysis alternate, the insight grew that discussions on the role of guidelines, applied to patients with multimorbidity, provided important information meriting deeper exploration on itself. This resulted in formulating the second, separate research question. The focus groups were guided by an experienced moderator, who used an interview guide. Interviews were transcribed verbatim. Data collection proceeded until saturation was reached. Data analysis was performed by two researchers using the constant comparison analysis technique.

Separate qualitative analyses were performed considering the two distinct research questions.

Chapter 5 described that applying a patient-centred approach is the main aim of GPs in their care for patients with multimorbidity. By individualising decisions and placing medical considerations in a broader perspective, they adjust their care to the specific person in front of them. Delivering integrated care helps to prevent fragmentation of care, which was identified by the participating GPs as an important risk when patients have multimorbidity. The existence of a personal relationship between doctor and patient, built over time, helps in the complex management of patients with multimorbidity, and may facilitate shared decision making. The combined presence of somatic and mental health conditions was especially perceived as a difficult combination in patients with multimorbidity, since diagnosis and management of somatic and mental health conditions may mutually influence one other. Applying a patient-centred approach helps to counteract some potential pitfalls of multimorbidity, but demands the flexibility to deviate from disease-specific management strategies in patients with multiple diseases.

In Chapter 6 it was described that guidance from guidelines was appreciated in general by GPs, but that they were perceived as insufficient to guide the complex care needed for patients with multimorbidity. They do not provide sufficient opportunity to take account of patients' personal circumstances, which was perceived as highly important in the care for patients with multimorbidity. Especially for the older patients with multimorbidity, preventative measures, often recommended in evidence-based guidelines, were considered inappropriate in many cases. GPs doubted the applicability of guidelines for patients with multimorbidity. GPs described that they complement the gaps in applicability and usefulness of guidelines for patients with multimorbidity by using their common sense. They formulated suggestions how the applicability of guidelines for patients with multimorbidity could be improved, for example by making a ranking of importance in guideline recommendations appropriate for (specific groups of) patients with multimorbidity. GPs practice evidence-based medicine for patients with multimorbidity by integrating clinical experience with the best available evidence.

Chapter 7 gave an overview of the results, and discussed the interpretation of the overall findings in this mixed methods thesis. It furthermore described the relevance of these findings in relation to the existing literature and addressed methodological issues. The implications from this thesis for research, guidelines and practice were discussed. It was concluded that more research is needed to gain better insight into patterns of comorbidity

and their consequences for patients, both on disease-specific and on generic outcomes. The primary care setting may be an ideal setting for ongoing research in multimorbidity since it can produce representative results. Blanks in relevant and applicable evidence for patients with multimorbidity will probably remain, and therefore it is important to provide patient-centred care to patients with multimorbidity, focusing on the needs, preferences, and risks of a specific patient. GPs may be perfectly suited to help a patient assign priorities, and to provide individualised, integrated, continuous care to patients with multimorbidity.

Nederlandse samenvatting

SAMENVATTING

Dit proefschrift beschreef multimorbiditeit in de eerste lijn met een focus op het perspectief van de huisarts. Er werd gebruik gemaakt van mixed methods. De doelstellingen waren:

- Het beschrijven van de prevalentie en incidentiedichtheid van comorbiditeit bij patiënten met diabetes type 2.
- Het exploreren van associaties tussen comorbiditeit en longitudinale diabetes controleparameters op de lange termijn bij patiënten met diabetes type 2.
- Het bestuderen van de overwegingen en belangrijkste doelen van huisartsen in hun zorg aan patiënten met multimorbiditeit, en het exploreren van factoren die hun handelen bij multimorbiditeit beïnvloeden.
- Het exploreren van de waarde die huisartsen toekennen aan richtlijnen als deze toegepast worden op patiënten met multimorbiditeit, en van de voordelen en belemmeringen die zij ervaren van het opvolgen van richtlijnen bij deze patiënten.

In het **eerste deel** van dit proefschrift werden de associaties tussen diabetes type 2 en chronische comorbide aandoeningen als een 'case study' beschreven. In het **tweede deel** van dit proefschrift werden de ervaringen van huisartsen met, en oplossingen in de dagelijkse praktijk voor het omgaan met multimorbiditeit beschreven.

In **Hoofdstuk 1** werd een introductie op het thema multimorbiditeit gegeven. Diverse problemen voortkomend uit multimorbiditeit werden geschetst, zowel voor patiënten als voor de praktijkvoering. De beschrijving van de ontwikkeling van kennis over multimorbiditeit in het onderzoeksveld en de resterende kennishiaten leidden tot de formulering van de onderzoeksvragen van dit proefschrift.

Hoofdstuk 2 beschreef de prevalentie en incidentiedichtheid van een grote verscheidenheid aan chronische comorbide aandoeningen in een representatief cohort van patiënten met diabetes type 2 in de eerste lijn. Hieruit bleek dat zowel concordante (gerelateerde, dat wil zeggen, cardiovasculaire) en discordante (ongerelateerde) comorbiditeit veelvuldig voorkwam. Op het moment dat diabetes werd vastgesteld had bijna 85% van deze patiënten een of meer andere chronische aandoeningen, en na exclusie van concordante cardiovasculaire aandoeningen gold dit nog voor ruim 70% van de patiënten. Uitgebreide comorbiditeit, gedefinieerd als drie of meer ziektes naast de diabetes, was aanwezig bij circa de helft of een kwart van de diabetespatiënten, wanneer alle soorten, respectievelijk alleen discordante comorbiditeit werd meegeteld. In het eerste jaar na de diabetes diagnose werd een eerste comorbide aandoening gediagnosticeerd bij een kwart van de patiënten die ten tijde van de diabetes diagnose nog geen comorbiditeit hadden.

Alleen chronische aandoeningen werden als comorbiditeit geteld. Voor ziektes die een chronisch beloop kunnen, maar niet hoeven te hebben, zoals jicht of migraine, werd chroniciteit op patiëntniveau vastgesteld, gebaseerd op informatie uit het elektronisch medisch dossier van patiënten. Ziektes werden gecategoriseerd in ziekteclusters, gebaseerd op de ICPC-classificatie, met aparte clusters voor oncologische en infectieuze aandoeningen. Prevalentie en incidentiedichtheid van comorbiditeit werd ook berekend voor ziekteclusters. De hoogste prevalenties ten tijde van de diabetes diagnose werden gevonden voor cardiovasculaire (64%) en musculoskeletale aandoeningen (31%). Deze studie liet zien dat de diabetespopulatie heterogeen is in termen van comorbiditeit, en dat de diabetespatiënt zonder (discordante) comorbiditeit relatief zeldzaam is. Daarom is de nagenoeg afwezige aandacht voor (discordante) comorbiditeit in evidence-based richtlijnen onterecht. Richtlijnen moeten beter kenbaar maken hoe comorbiditeit kan interfereren met de behandeling van diabetes – wat met name het geval kan zijn bij discordante comorbiditeit – en zouden hun aanbevelingen hierop moeten aanpassen.

In hetzelfde eerstelijns cohort van patiënten met diabetes type 2 werden in **Hoofdstuk 3** de associaties tussen longitudinale diabetes controleparameters, en het aantal en specifieke soorten van comorbiditeit geëxploreerd. Met behulp van een mixed model analysetechniek werden longitudinale trends van HbA1c en systolische bloeddruk (SBD) gedurende vijf jaar follow-up vergeleken tussen groepen diabetespatiënten met verschillende comorbiditeit profielen. De simpele som van comorbide aandoeningen liet geen ongunstige associatie met de trends van diabetes controleparameters over vijf jaar zien, maar bepaalde soorten comorbiditeit wel. Diabetespatiënten met comorbide musculoskeletale aandoeningen hadden statistisch significant hogere HbA1c waarden na vijf jaar, met lagere waarden ten tijde van de diabetes diagnose, vergeleken met patiënten zonder musculoskeletale aandoeningen. Diabetespatiënten met comorbide cardiovasculaire aandoeningen hadden significant verhoogde waarden van de SBD, aanhoudend vanaf de diabetes diagnose, in vergelijking met patiënten zonder comorbide cardiovasculaire aandoeningen. Het aantal comorbide aandoeningen was significant geassocieerd met de trend van SBD (niet die van HbA1c) over vijf jaar, met de hoogste waarden na vijf jaar bij diabetespatiënten zonder comorbiditeit, en met effectmodificatie door de socio-economische status. Uit het exploratieve, observationele design van deze studie kunnen geen causale verbanden worden afgeleid. Verondersteld werd dat de verminderde mogelijkheid tot fysieke inspanning de verklaring kon zijn voor de oplopende HbA1c waardes over vijf jaar bij de patiënten met comorbide musculoskeletale aandoeningen, en dat de concordantie van cardiovasculaire comorbiditeit de resultaten van deze patiëntengroep op de longitudinale SBD uitkomsten verklaarde. De vaststelling dat niet slechts de som der ziektes een negatieve invloed

op de diabetes controleparameters had, maar aanwezigheid van specifieke typen comorbiditeit wel, benadrukt dat de diabeteszorg die door huisartsen geleverd wordt onderdeel is van algemene gezondheidszorg gericht op 'personen als geheel', dat wil zeggen 'persoonsgerichte zorg'. Blijkbaar intervenieerde de patiënt-specifieke context. Huisartsen integreerden ziekte-specifieke en generieke patiëntkarakteristieken en behandeldoelen in de zorg voor diabetes. Na vervolgonderzoek van de geobserveerde patronen kunnen deze bevindingen bijdragen aan de ontwikkeling van gepersonaliseerde diabetesbehandeling, door verschillende behandelmogelijkheden te formuleren die passend zijn voor diabetespatiënten met een specifiek comorbiditeit profiel.

In **Hoofdstuk 4** werden in het cohort met diabetes type 2 patiënten associaties tussen comorbide COPD en longitudinale diabetes controleparameters gedurende vijf jaar follow-up geëxploreerd. Met mixed model analyses werden trends in HbA1c en SBD vergeleken tussen patiënten met en zonder comorbide COPD. Met subgroep effect analyses werd, onder aan- of afwezigheid van COPD, potentiële effectmodificatie van deze trends door leeftijd, geslacht, body mass index en socio-economische status geëxploreerd. Gevonden werd dat diabetespatiënten met comorbide COPD andere trends van SBD over vijf jaar hadden dan patiënten zonder COPD, met effectmodificatie door socio-economische status en body mass index. In tegenstelling tot diabetespatiënten zonder COPD, bij wie een hogere body mass index geassocieerd was met hogere SBD waarden, werd bij diabetespatiënten met comorbide COPD de SBD trend meer door de socio-economische status dan door de body mass index bepaald. Diabetes type 2 en COPD, twee veel voorkomende chronische aandoeningen met een substantieel gecombineerd optreden, interfereren met elkaar. Vervolgonderzoek is nodig om de complexe associaties tussen comorbiditeit bij diabetes en COPD, diabetes controleparameters en overige patiëntkarakteristieken verder te ontrafelen; en om vast te stellen hoe deze vertaald dienen te worden naar praktische aanbevelingen. Wat duidelijk is, is dat de interactie tussen deze twee veel voorkomende aandoeningen aandacht van zorgprofessionals die zorg dragen voor patiënten met deze aandoening(en) vereist, en dat comorbiditeit erkend moet worden als een patiëntkarakteristiek met mogelijke invloed op ziekte-specifieke uitkomstmaten van een index-ziekte.

Het **tweede deel** van dit proefschrift bevatte kwalitatief onderzoek. Een focusgroep studie werd uitgevoerd met een 'purposive sample' van Nederlandse huisartsen om heterogeniteit in karakteristieken als leeftijd, geslacht en urbanisatie onder de deelnemers te verkrijgen. Het eerste doel was te exploreren wat hun overwegingen en belangrijkste doelen in de zorg voor patiënten met multimorbiditeit zijn, en factoren die dit handelen beïnvloeden. Verkennen van de waarde die huisartsen aan richtlijnen toekennen als

deze worden toegepast op patiënten met multimorbiditeit, en welke voor- en nadelen zij ervaren van het volgen van de richtlijnen bij deze patiëntengroep, was het tweede doel. Tijdens het iteratieve kwalitatieve proces, waarbij dataverzameling en analyse elkaar afwisselen, groeide het inzicht dat discussies over de rol van richtlijnen, toegepast op patiënten met multimorbiditeit, belangrijke informatie opleverden die op zichzelf nadere exploratie verdiende. Dit resulteerde in het formuleren van de tweede, separate onderzoeksvraag. De focusgroepen werden geleid door een ervaren moderator die gebruik maakte van een interview guide. Interviews werden verbatim getransscribeerd. Dataverzameling werd gecontinueerd totdat saturatie was bereikt. Analyse van de data werd uitgevoerd door twee onderzoekers die gebruik maakten van de analysemethode met constante vergelijking. Voor de twee verschillende onderzoeksvragen werden aparte analyses uitgevoerd.

In **Hoofdstuk 5** werd beschreven dat het hoofddoel van huisartsen bij hun zorgverlening aan patiënten met multimorbiditeit het aanwenden van een patiëntgerichte benadering is. Door beslissingen te individualiseren en medische overwegingen in een breder perspectief te plaatsen, stemmen zij hun zorg af op de specifieke patiënt tegenover hen. Het verlenen van geïntegreerde zorg helpt om versnippering, wat door de deelnemende huisartsen werd aangemerkt als een belangrijk risico bij multimorbiditeit, te voorkomen. Aanwezigheid van een persoonlijke relatie tussen arts en patiënt die door de jaren heen is opgebouwd helpt bij de complexe zorg voor patiënten met multimorbiditeit, en kan shared decision making faciliteren. Het bestaan van zowel somatische als psychische aandoeningen tegelijkertijd werd ervaren als een moeilijke combinatie, aangezien de diagnostiek en behandeling van somatische en psychische aandoeningen elkaar over en weer kunnen beïnvloeden. Het toepassen van een patiëntgerichte benadering helpt om een aantal potentiële valkuilen bij multimorbiditeit te voorkomen, maar vereist de flexibiliteit om een ziektegerichte benadering te verlaten bij patiënten met meerdere ziektes.

Hoofdstuk 6 beschreef dat sturing uit richtlijnen in het algemeen werd gewaardeerd door huisartsen, maar dat richtlijnen als niet toereikend werden ervaren om de complexe zorg die nodig is bij multimorbiditeit te kunnen bieden. Ze bieden onvoldoende mogelijkheid om rekening te houden met de persoonlijke omstandigheden van patiënten, en dit werd juist als zeer belangrijk ervaren in de zorg voor patiënten met multimorbiditeit. Met name voor oudere patiënten met multimorbiditeit werden preventieve maatregelen, die vaak worden aanbevolen in evidence-based richtlijnen, nogal eens als ongepast beschouwd. Huisartsen twijfelden aan de toepasbaarheid van richtlijnen voor patiënten met multimorbiditeit. Ze beschreven dat zij hiaten in bruikbaarheid en toepasbaarheid

van richtlijnen voor patiënten met multimorbiditeit aanvullen door hun gezonde verstand te gebruiken. Huisartsen gaven suggesties hoe de toepasbaarheid van richtlijnen voor patiënten met multimorbiditeit verbeterd zou kunnen worden, bijvoorbeeld door een hiërarchie aan te brengen in het belang van de aanbevelingen in richtlijnen die van toepassing zijn voor (specifieke groepen van) patiënten met multimorbiditeit. Door klinische ervaring met het best beschikbare bewijs te combineren, passen huisartsen evidence-based medicine toe bij patiënten met multimorbiditeit.

Hoofdstuk 7 gaf een overzicht van de resultaten uit dit proefschrift en besprak de interpretatie van de bevindingen, die met behulp van mixed methods werden verkregen. Ook werd de relevantie van deze bevindingen in relatie tot de bestaande literatuur beschreven en werden methodologische kwesties besproken. De betekenis voor onderzoek, richtlijnen en praktijk werd besproken. Geconcludeerd werd dat meer onderzoek nodig is om beter inzicht te verkrijgen in de patronen van comorbiditeit en de consequenties hiervan voor patiënten, zowel op ziekte-specifieke als op generieke uitkomstmaten. De eerste lijn kan een ideale setting zijn voor aanhoudend onderzoek naar multimorbiditeit omdat hier representatieve resultaten verkregen kunnen worden. Hiaten in relevante en toepasbare wetenschappelijke kennis voor patiënten met multimorbiditeit zullen waarschijnlijk blijven bestaan. Daarom is het belangrijk om patiëntgerichte zorg te verlenen aan patiënten met multimorbiditeit, die zich richt op de behoeften, voorkeuren en risico's van een specifieke patiënt. Huisartsen zijn goed toegerust om een patiënt te helpen bij het stellen van prioriteiten, en om geïndividualiseerde, geïntegreerde, continue zorg te verlenen aan patiënten met multimorbiditeit.

Dankwoord

DANKWOORD

Het doorlopen van dit promotietraject is teamwork geweest. De steun van de volgende mensen is hierbij heel belangrijk geweest voor mij.

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Beste Toine, jouw bevlogenheid is inspirerend. Je bent een betrokken huisarts en in deze rol ben je altijd een voorbeeld voor me geweest. Maar daarnaast was jij degene die me heeft aangezet om onderzoek te gaan doen. Het begon met een klein projectje en bleek de aanzet tot een promotietraject. Je jarenlange praktijkervaring, waaronder die met multimorbiditeit, en je kennis van de CMR zijn hierbij zeer waardevol geweest. Ik bewonder je tomeloze energie en je scherpe geheugen, en ik waardeer je betrokkenheid, je benaderbaarheid en je nooit aflatende attentie.

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maar nooit was een vraag van mij te gek en altijd was je bereid tot geduldige uitleg. Ontzettend bedankt hiervoor.

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Dear members of the Doctoral Thesis Committee, thank you for the effort to evaluate my thesis. I am looking forward to our discussions during my defence.

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De ‘eerste generatie’ aiotho’s wil ik bedanken voor het uitvinden van het wiel en de goede adviezen aan de ‘tweede generatie’ waartoe ik mezelf reken. Mede-aiotho’s ‘van mijn lichting’, door onze immer wisselende aanwezigheid, volle agenda’s en verspreide werkplekken zagen we elkaar veelvuldig óf zelden, maar het was altijd fijn om van gedachten te wisselen met gelijkgestemden! Wouter, jij was mijn maatje van het eerste uur, altijd behulpzaam en geïnteresseerd. Maartje, het was fijn om met jou samen de focusgroepen te analyseren, dank daarvoor. Sabine, ik ken weinig mensen die zo attent zijn als jij. Eerst wisselden we ervaringen uit over de combi onderzoek en opleiding en daarna leende je me je zwangerschapskleding.
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Om onderzoek te kunnen doen naar multimorbiditeit in de huisartspraktijk moet je weten hoe het er in die praktijk aan toe gaat. En wat is het vak van de huisarts toch prachtig. Wessel, met groot enthousiasme begon je eraan mij te leren kijken en denken als een huisarts. Erna en Charles, jullie mochten die ‘klus’ afmaken. Ik ben blij dat ik drie opleiders heb getroffen bij wie het huisartsenbloed door de aderen stroomt en met wie ik veel van gedachten heb kunnen wisselen over de zorg voor mensen die van alles mankeren. Dank voor de ruimte die jullie me hebben geboden mijn opleiding te combineren met onderzoek doen. Erna en Charles, wat leuk dat we uiteindelijk HAGRO collega’s zijn geworden!

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List of publications

LIST OF PUBLICATIONS

Peer reviewed

Luijks H, Biermans M, Bor H, Van Weel C, Lagro-Janssen T, De Grauw W, Schermer T. The effect of comorbidity on glycemic control and systolic blood pressure in type 2 diabetes: a cohort study with 5 year follow-up in primary care. *PLoS One* 2015; *in press.*

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Luijks H. Comorbiditeit bij diabetes type 2. *Huisarts Wet* 2014; 253.

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Curriculum Vitae

CURRICULUM VITAE

Hilde Luijks was born on 6 January 1983 in Drunen as the daughter of Kees and Elly Luijks. Her first year of secondary school was at the d'Oultremontcollege in Drunen, the following years were at the dr. Mollercollege in Waalwijk, where she graduated in 2001. Later that year she started her studies in medicine at the Radboud university medical center in Nijmegen. During her studies, she was active in the Medical Faculty Association Nijmegen.

Hilde finished medical training in 2007. She first worked as a clinical house officer on the emergency care department at the Jeroen Bosch Ziekenhuis in 's-Hertogenbosch. In 2009, she started the vocational training programme in general practice at the Radboud university medical center. Halfway the first year of her GP residency, she decided to combine this with scientific research as a PhD candidate. In this so-called 'aiotho' programme, GP residency and research activities alternated or were combined. Her research resulted in this thesis.

Hilde finished the GP vocational training in 2013 and now works as a GP in the academic health centre Thermion in Lent, Nijmegen.

She lives together with Stefan Bouwense and their son Joost.

Appendix A

Chronic diseases regarded as comorbidity

This Appendix contains supplementary data to Chapter 2

CHRONIC DISEASES ('OBLIGATORY CHRONIC DISEASES')

Total number: 67

E-list code	Disease	ICPC equivalent
0044	HIV; AIDS	B90
0500	Cancer of the mouth / pharynx	D77.02, D77.03, R85
0510	Oesophageal cancer	D77.01
0520	Cancer of the stomach	D74
0530	Colon cancer	D75
0540	Rectal cancer	D75
0550	Pancreatic cancer	D76
0560	Laryngeal / throat cancer	R85
0570	Lung / bronchial cancer	R84
0580	Breast cancer	X76
0590	Uterine cervical cancer	X75
0600	Endometrial cancer	X77.01
0610	Prostate cancer	Y77
0620	Bladder cancer	U76
0632	Ovarian cancer	X77.02
0639	Genitourinary cancer, other	U75, U77, X77, Y78
0650	Brain cancer / tumour	N74
0660	Hodgkin disease	B72.01
0670	Leukaemia	B73
0681	Lymphoma / multiple myeloma	B74.01
0682	Metastases; unknown origin	A79
0689	Carcinoma, other	D77.04, L71, T71, W72
0640 + 0641 + 0642 + 0649	Skin cancer	S77
0890	Hypothyroidism	T86
1101	Pernicious anaemia	B81.02
1141	Polycythaemia	B75
1142	Haemophilia	B83.01
1192	Haemolytic anaemia, congenital	B78
1250	Schizophrenia	P72
1270	Alzheimer's disease	P70
1380	Personality disorder	P80
1401 + 1402	Mental retardation	P85
1403	Child development disorders, pervasive	P99
1551	TIA (transient ischemic attack)	K89
1559	CVA (cerebrovascular accident)	K90
1560	MS (multiple sclerosis)	N86

1570	Parkinson's disease	N87.01
1800	Glaucoma	F93
1811	Blindness / amblyopia	F94
1841	Cholesteatoma	H74.03
1880	Otosclerosis	H83
1890	Deafness	H84, H86
2080	Heart valve disease	K83
2090	Heart valve disease (rheumatic)	K71.02
2110	Myocardial infarction	K75
2120	Angina pectoris	K74
2131	(Congestive) heart failure	K77
2132	Atrial fibrillation / flutter	K78
2133	Pulmonary heart disease	K82
2180 + 2181 + 2189	Hypertension	K86, K87
2231	Intermittent claudication	K92.01
2480	COPD (chronic obstructive pulmonary disease)	R95
2530	Pneumoconiosis	R99.06
2540	Bronchiectasis	R91.02
2852	Crohn's disease; ulcerative colitis	D94
2881	Hepatic cirrhosis	D97
3820	Psoriasis	S91
4050 + 4051 + 4052	Rheumatoid arthritis; ankylosing spondylarthritis	L88.01, L88.02
4061	Osteoarthritis, hip	L89
4062	Osteoarthritis, knee	L90
4063	Lumbar osteoarthritis	L84
4064	Osteoarthritis, cervical spine	L84.01
4069	Osteoarthritis, other	L91
4154	Osteoporosis	L95.02
4300	Multiple congenital abnormalities	A90
4310	Spinal dysraphism	N85.01
4389	Down syndrome / other specified congenital abnormalities	A90(.01)

CONDITIONALLY CHRONIC DISEASES[1]

Total number: 63

Code	Disorder	ICPC equivalent
0010	Pulmonary tuberculosis	R70 (ex. A70)
0020	Tuberculosis, *other organs*	A70 (ex. R70)
0030	Syphilis	X70 / Y70
0162	Hepatitis B	D72.02
0164	Hepatitis C	D72.03
0169	Hepatitis	D72
0460	Sarcoidosis	R83.02
0470	Lyme disease	A78.05
0631	Testis cancer	Y78.02
0710	Uterine fibroid	X78.01
0821	Neoplasm malignant / benign	S80
0860	Asthma	R96
0880	Hyperthyroidism	T85
0930	Gout	T92
0949	Endocrine disease, other	T99
1109	Anaemia, *other deficiency*	B81
1221	Lymphadenitis, chronic, *not specified*	B71
1260 + 1341 + 1342	Depressive disorder	P76
1280	Organic psychosis	P71
1290	Psychosis	P98
1311	Anorexia nervosa	T06
1312	Somatoform disorder	P75
1321	Phobia	P79.01
1322	Anxiety disorder	P74
1330	Obsessive-compulsive disorder	P79.02
1351	Irritable bowel syndrome	D93
1359	(Chronic) functional somatic symptoms[2]	P01, P78
1580	Epilepsy	N88
1590	Migraine	N89
1790	Cataract	F92
1849	Chronic otitis media	H74.01
1860	Meniere disease	H82.01
2072	Restless legs syndrome	N04

2100	Rheumatic fever	K71.01
2232	Pulmonary embolism	K93
2239	Peripheral arterial disease; Raynaud's disease	K99
2240	Varicose veins; venous insufficiency	K95, K99.04
2280	Varicose ulcer	S97.01
2472	Bronchitis	R78
2500	Chronic sinusitis	R75.02
2764	Oesophageal disease	D84
2770	Stomach ulcer	D86.01
2780	Duodenal ulcer	D85
2790	Peptic ulcer, *other*	D86
2841	Diaphragmatic hernia	D90
2851	Colonic diverticula; diverticulitis	D92
2884	Pancreatic disease; other	D99
3101	Glomerulonephritis	U88
3102	Glomerulonephrosis	U88
3120	Urinary calculi / urinary tract stones	U95
3140	Urinary tract infection, chronic / recurrent	U71
3180	Prostatic hyperplasia / hypertrophy	Y85
3390	Urinary incontinence	U04
3722	Hidradenitis	S92.02
3780	Seborrhoeic dermatitis	S86
3790	Atopic dermatitis	S87
3801	Contact dermatitis	S88.01
3900	Chronic skin ulcer	S97
4152	Polymyalgia rheumatica; giant cell arteritis	K99.05, L99.12
4170	Autoimmune diseases	K99, L99, S99, U99
4320	Hydrocephalus	N85.02
4330	Congenital cardiovascular anomaly	K73
4340	Cleft palate	D81.01

[1]Note: For conditionally chronic diseases, only episodes assigned 'ongoing attention' are counted as chronic disease.

[2]Chronic functional somatic symptoms are chronic symptoms in patients who experience functional impairment and for which a medical (organic) explanation cannot be found. GPs in the Continuous Morbidity Registration tended to classify patients as such after three episodes of presenting with functional somatic symptoms. (Reference: Olde Hartman TC, Lucassen PL, Van de Lisdonk EH, Bor HH, Van Weel C: Chronic functional somatic symptoms: a single syndrome? *Br J Gen Pract* 2004, **54:** 922-927.)

Appendix B

Clusters of chronic comorbidity

This Appendix contains supplementary data to Chapter 2

Cluster of chronic diseases	Disease
Cardiovascular	TIA (transient ischemic attack)
	CVA (cerebrovascular accident)
	Heart valve disease
	Myocardial infarction
	Angina pectoris
	(Congestive) heart failure / heart decompensation
	Atrial fibrillation / flutter
	Hypertension
	Intermittent claudication
	Peripheral arterial disease; Raynaud's disease[1]
	Varicose veins / venous insufficiency[1]
	Congenital heart defects[1]
Musculoskeletal	Rheumatoid arthritis; ankylosing spondylarthritis
	Osteoarthritis, hip
	Osteoarthritis, knee
	Lumbar osteoarthritis
	Osteoarthritis, cervical spine
	Osteoarthritis, other
	Polymyalgia rheumatica; giant cell arteritis[1]
	Osteoporosis
Mental health	Schizophrenia
	Depressive disorder[1]
	Alzheimer's disease
	Organic psychosis[1]
	Psychosis[1]
	Phobia[1]
	Anxiety disorder[1]
	Obsessive-compulsive disorder[1]
	(Chronic) functional somatic symptoms[1]
	Personality disorder
	Mental retardation
Eye & Ear	Cataract[1]
	Glaucoma
	Blindness / amblyopia
	Chronic otitis media[1]
	Meniere disease[1]
	Otosclerosis
	Deafness

(Male and female) urogenital	Uterine fibroid / uterine leiomyoma[1]
	Glomerulonephritis[1]
	Glomerulonephrosis[1]
	Urinary calculi / urinary tract stones[1]
	Urinary tract infection, chronic / recurrent[1]
	Prostatic hyperplasia / hypertrophy[1]
	Urinary incontinence[1]
Respiratory	Sarcoidosis[1]
	Asthma[1]
	COPD (chronic obstructive pulmonary disease)
	Chronic sinusitis[1]
	Pneumoconiosis
	Bronchiectasis
Skin	Hidradenitis[1]
	Seborrhoeic dermatitis[1]
	Atopic dermatitis[1]
	Contact dermatitis[1]
	Psoriasis
	Chronic skin ulcer[1]
Digestive	Irritable bowel syndrome[1]
	Oesophageal disease[1]
	Stomach ulcer[1]
	Duodenal ulcer[1]
	Diaphragmatic hernia[1]
	Colonic diverticula; diverticulitis[1]
	Crohn's disease; ulcerative colitis
	Hepatic cirrhosis
	Pancreatic disease; other[1]
	Cleft palate[1]
Endocrine and metabolic	Hyperthyroidism[1]
	Hypothyroidism
	Gout[1]
	Endocrine disease, other[1]
Neurological	MS (multiple sclerosis)
	Parkinson's disease
	Epilepsy[1]
	Migraine[1]
Blood(forming organs) and lymphatics	Pernicious anaemia
	Anaemia, *other deficiency*[1]
General and unspecified	Down syndrome / other specified congenital abnormalities

Infectious	Pulmonary tuberculosis[1]
	Syphilis[1]
Malignancies	Cancer of the mouth / pharynx
	Oesophageal cancer
	Cancer of the stomach
	Colon cancer
	Rectal cancer
	Pancreatic cancer
	Laryngeal / throat cancer
	Lung / bronchial cancer
	Breast cancer
	Uterine cervical cancer
	Endometrial cancer
	Prostate cancer
	Bladder cancer
	Ovarian cancer
	Genitourinary cancer, other
	Skin cancer
	Brain cancer / tumour
	Leukaemia
	Lymphoma / multiple myeloma
	Metastases; unknown origin
	Carcinoma, other

Note: Only chronic comorbid diseases occurring at least once in the study population were classified into clusters.
[1]Conditionally chronic disease: requiring physician-assigned 'ongoing episodes' at the patient level in order to be assigned as chronic disease.

Appendix C

Classification of comorbidity

This Appendix contains supplementary data to Chapter 3

CLASSIFICATION OF COMORBIDITY

The following clusters of chronic diseases were distinguished:

- Cardiovascular disease
- Malignancy
- Musculoskeletal disease
- Mental health disease
- Respiratory disease
- Eye and ear disease
- (Male and female) urogenital disease
- Skin disease
- Digestive system disease
- Endocrine and metabolic disease
- Neurological disease
- Blood(forming organs) and lymphatics disease
- Infectious disease
- General and unspecified disease

Each disease cluster contains several chronic diseases. Within any cluster of diseases, presence of at least one chronic disease classified in this cluster was required in order to be counted as presence of this disease cluster in a particular patient. For each separate cluster it was defined whether or not a particular patient classified for this disease cluster. Any single chronic disease present in any of the abovementioned clusters contributed to the total sum of comorbidity as distinguished in this study ('number of comorbid diseases').

This study included only chronic diseases as comorbidity. Some diseases can be regarded as invariably chronic diseases (e.g. rheumatoid arthritis, schizophrenia). Other diseases may have a chronic course in a particular patient but do not necessarily do so in all cases (e.g. gout, migraine, depression). These diseases were defined as 'conditionally chronic' diseases and were included as comorbidity in this study only when it had a chronic course in this particular patient. These methods have been elaborated in a previous paper of the same research group.[1]

In the current study, five selected clusters of diseases were analysed separately, in addition to the analysis of the number of comorbid diseases. These disease clusters were cardiovascular disease, malignancy, musculoskeletal disease, mental health disease, and COPD as selected disease from the respiratory disease cluster.

The following diseases were included within the disease clusters of special interest (conditionally chronic disease are marked with an asterisk*):

Cardiovascular disease:
- Angina pectoris
- Atrial fibrillation / flutter
- Myocardial infarction
- (Congestive) heart failure
- Intermittent claudication
- TIA (transient ischemic attack)
- CVA (cerebrovascular accident)
- Heart valve disease
- Peripheral arterial disease / Raynaud's disease*
- Chronic venous insufficiency / chronic varicosis*
- Congenital heart defects*
- Hypertension†

†In the current study, with SBP as one of the primary outcome measures, presence of hypertension as diagnostic label in the CMR registry had to be complemented with at least one other cardiovascular disease diagnostic label for patients to be analysed longitudinally within the cardiovascular disease cluster.

Malignancy:
- Breast cancer
- Prostate cancer
- Endometrial cancer
- Skin cancer (only the types with potential to metastasise, e.g. basal cell carcinoma was excluded)
- Colon cancer
- Rectal cancer
- Lung / bronchial cancer
- Bladder cancer
- Ovarian cancer
- Uterine cervical cancer
- Brain cancer
- Leukaemia
- Lymphoma / multiple myeloma
- Cancer of the stomach
- Oesophageal cancer
- Pancreatic cancer
- Cancer of the mouth / pharynx

- Laryngeal / throat cancer
- Other specified types of cancer or metastases of unknown origin

Musculoskeletal disease:
- Rheumatoid arthritis; ankylosing spondylarthritis
- Osteoarthritis of the knee
- Osteoarthritis of the hip
- Osteoarthritis of the lumbar or cervical spine
- Other specified osteoarthritis
- Osteoporosis
- Polymyalgia rheumatica; giant cell arteritis*

Mental health disease:
- Depression*
- Anxiety disorder*
- Personality disorder
- Obsessive-compulsive disorder*
- Schizophrenia
- Psychosis*
- Phobia*
- (Chronic) functional somatic symptoms*
- Alzheimer's disease
- Mental retardation

Respiratory disease:
As fifth separate disease group of special interest, COPD as a single disease was analysed for associations with the longitudinal study outcomes, since within the cluster of respiratory diseases, COPD constituted the large majority of diseases (79%), and with that its prevalence was large enough to be studied on itself. This ensured good homogeneity within this comorbidity group, since COPD has a distinct therapeutic approach from the other diseases. The following diseases were considered within the entire cluster of respiratory diseases and could contribute to the total number of comorbid diseases:
- COPD (chronic obstructive pulmonary disease)
- Sarcoidosis*
- Asthma*
- Pneumoconiosis
- Bronchiectasis
- Chronic sinusitis*

REFERENCES

1. Luijks H, Schermer T, Bor H, van Weel C, Lagro-Janssen T, Biermans M*, et al.* Prevalence and incidence density rates of chronic comorbidity in type 2 diabetes patients: an exploratory cohort study. *BMC Med* 2012; **10**: 128.

RIHS PhD portfolio

RIHS PHD PORTFOLIO

Institute for Health Sciences
Radboudumc

Name PhD student: HDP (Hilde) Luijks
Department: Primary and Community Care
Graduate School: Radboud Institute for Health Sciences

PhD period: 01-09-2009 till 09-11-2015
(2 years + 3,5 months as 1.0 fte equivalent – combined programme with GP residency)
Promotor(s): Prof. Chris van Weel, Prof. Toine Lagro-Janssen
Co-promotor(s): Dr Tjard Schermer, Dr Marion Biermans

	Year(s)	ECTS
TRAINING ACTIVITIES		
a) Courses & Workshops		
- PubMed course	2009	0.1
- SPSS introduction course	2010	0.2
- Biometrics	2010-2011	3.0
- Academic writing	2011	2.0
- Qualitative research	2010	1.0
- Presentation skills	2011	1.5
b) Seminars & lectures^		
- European General Practice Research Network (EGPRN) conference Multimorbidity, Dubrovnik	2009	1.0
- NHG congres ouderenzorg en multimorbiditeit	2009	0.2
- NHG Wetenschapsdag	2011	0.2
c) Symposia & congresses^		
- Nijmegen Monitoring Project (NMP) meetings: oral presentations	2010, 2015	0.3
- North American Primary Care Research Group (NAPCRG), Banff: oral presentation	2011	2.0
- NHG Wetenschapsdag, Maastricht: oral and poster presentation	2012	1.5
- International Primary Care Respiratory Group (IPCRG) conference, Athens: oral presentation	2014	0.2
- NHG Wetenschapsdag, Groningen: oral presentation	2014	0.2
d) Other		
- Journal club, Department Primary and Community Care (including oral presentations)	2010-2013	2.0
- Research visit Scotland	2014	3.5
- Reviewing scientific papers for multiple journals	2010-2015	0.8
- Reviewing abstracts for NHG Wetenschapsdag	2011	0.6
- Promovendi Opleidings Commissie, researchschool CaRe	2010-2014	0.3
TEACHING ACTIVITIES		
e) Lecturing		
- Lecturing Evidence Based Medicine (EBM), medical students Radboudumc	2011-2012	0.3
- GP residency programme, Radboudumc: EBM	2010-2013	0.3
- Assessment Critically Appraised Topics (CATs), GP residents Radboudumc	2014, 2015	0.6
f) Supervision of internships / other		
- Supervision research internship (Renee vd Sande)	2012	1.0
- Supervision research internship (Ireen Hoogstraten)	2014	1.0
TOTAL		24,1

^Indicate oral or poster presentation

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